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"Problems in Surgery"

The August Number of the *Surgical Clinics of North America* comes from the Mayo Clinic and is devoted entirely to Problems in Surgery.

There are *22 Clinics* in this August Number dealing with such problems as Treatment of Ununited Fractures of the Hip, Chronic Sclerosing Osteitis, Plasma and Blood in Treatment of Shock from Burns, Chronic Nonspecific Tenosynovitis and Peritendinitis, Shock in Relation to Anesthetic Management, Powdered Erythrocytes for Dressings of Wounds and Ulcers, the Rh Factor, Broncholithiasis, Pulmonary Abscess, Traumatic Injuries of the Abdomen, Pain Produced by Intraspinal Tumor Simulating Pain Caused by Gallbladder Disease, Headache and Paroxysmal Hypertension, Renal Ectopia, Hair-bearing Scalp Flap for Repair of Unilateral Scalp Defects, etc.

As an aid to sound diagnosis and as a guide to effective treatment, this August Number from the Mayo Clinic is a typical example of the kind of practical assistance that subscribers get year in and year out from the *Surgical Clinics of North America.*

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PENICILLIN

ITS USEFULNESS, LIMITATIONS, DIFFUSION AND DETECTION, WITH ANALYSIS OF 150 CASES IN WHICH IT WAS EMPLOYED

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DONALD R. NICHOLS, M.D.
AND
DOROTHY H. HEILMAN, M.D.
ROCHESTER, MINN.

The introduction of penicillin for treatment of bacterial infections is one of the most important developments in chemotherapy. The relative lack of toxicity of penicillin for most tissues is one of its great advantages. This lack of toxicity was apparent to Fleming [1] and to Florey and his associates.[2] It was further evident from studies carried out in our laboratories, which began early in 1941,[3] that penicillin was a highly antibacterial substance and at the same time possessed very low toxicity for tissue as measured by means of tissue culture methods. Although penicillin is exceedingly effective in treatment of some infections, it is ineffective against many others. One of the essential requirements for successful treatment of bacterial infections with penicillin is to limit its use to infections due to those pathogens which are known to be susceptible. At present the susceptible and the insusceptible organisms are essentially those listed in table 1. As the work progresses, other organisms undoubtedly will be added to the list.

The successful use of penicillin is attended by other problems not commonly encountered in the use of therapeutic agents. Penicillin therapy should be confined to institutions as long as it is necessary to administer the material intravenously or intramuscularly. Penicillin cannot be administered by mouth, because it is destroyed by the gastric acids. Neither can it be administered intracolonically, since it is destroyed by certain organisms present in the fecal stream.

The large scale preparation of penicillin has been accompanied by many difficulties which have necessitated careful control of release of the material. Because penicillin is extremely labile, it must be protected during its preparation against heat, changes in the p_H of the surrounding mediums, oxidizing agents and certain micro-organisms which elaborate substances which result in loss of potency of penicillin.

METHODS OF ADMINISTRATION

Local Application.—The broth filtrates of cultures of Penicillium notatum which contain penicillin were applied locally by Fleming [1] as early as 1929. In 1940 the Oxford investigators [2] reported the successful preparation of a purified penicillin which proved suitable for experimental studies and for treatment of infections due to susceptible organisms. Both the sodium and the calcium salts have been used for local treatment, but the calcium salt is more satisfactory. For local treatment of wounds involving soft tissue and bone and for topical application to infected surfaces, saline solutions containing 250 Oxford units per cubic centimeter are suitable. Recently the British investigators [4] have used penicillin locally in two other forms: 1. If a dry substance is desired, weighed amounts of penicillin are ground with sulfanilamide in a mortar until a homogeneous powder results. On occasions the final mixture contains as much as 5,000 Oxford units of penicillin per gram. The report by Ungar [5] suggests that penicillin and sulfonamides may have a synergistic effect. 2. Another preparation which the British have applied locally is a cream containing lanette wax, which contains 100 to 250 units of penicillin per gram.

In treatment of severe and extensive inflammatory lesions, uniformly satisfactory results are more likely to be obtained by systemic penicillin therapy alone or this in combination with local therapy.

Intrathoracic Instillation.—In treatment of suppurative intrathoracic disease, such as empyema, it is desirable to supplement parenteral therapy with instillation of penicillin into the pleural space. In many instances empyema thus can be satisfactorily treated without resorting to surgical drainage. For this purpose, as a rule, 30,000 to 40,000 Oxford units in 30 to 40 cc. of isotonic solution of sodium chloride can be instilled directly following thoracentesis. This procedure is carried out once every twenty-four to forty-eight hours.

Intra-Articular Instillation.—Recently our studies have indicated that fairly adequate antibacterial amounts of penicillin reach the joint fluid following intramuscular or intravenous administration of the material to patients suffering with acute or subacute suppurative disease of joints. The concentration of penicillin in the joint fluid is in some instances approximately half that in the blood. If it is desirable to supplement systemic therapy, however, instillation of penicillin into the joint

From the Division of Medicine (Drs. Herrell and Nichols) and the Division of Clinical Pathology (Dr. Heilman), Mayo Clinic.

Read before the Section on Miscellaneous Topics, Sessions for the General Practitioner, at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

Part of the penicillin used in these studies has been furnished by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

1. Fleming, Alexander: On the Antibacterial Action of Cultures of Penicillium, with Special Reference to Their Use in Isolation of B. Influenzae, Brit. J. Exper. Path. **10**: 226-236 (June) 1929.

2. Chain, E.; Florey, H. W.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J., and Sanders, A. G.: Penicillin as a Chemotherapeutic Agent, Lancet **2**: 226-228 (Aug. 24) 1940.

3. Heilman, Dorothy H., and Herrell, W. E.: Comparative Antibacterial Activity of Penicillin and Gramicidin: Tissue Culture Studies, Proc. Staff Meet., Mayo Clin. **17**: 321-327 (May 27) 1942; Comparative Bacteriostatic Activity of Penicillin and Gramicidin, abstr. J. Bact. **43**: 12-13 (Jan.) 1942.

4. Florey, H. W., and Cairns, H.: Penicillin in War Wounds: A Report from the Mediterranean, Lancet **2**: 742-745 (Dec. 11) 1943.

5. Ungar, J.: Synergistic Effect of Paraaminobenzoic Acid and Sulfapyridine on Penicillin, Nature, London **152**: 245-246 (Aug. 28) 1943.

is not accompanied by any serious effects. We have instilled as much as 20,000 Oxford units in 10 cc. of isotonic solution of sodium chloride directly into a septic joint after aspiration has been performed. Studies on the length of time that penicillin will remain in the joint following instillation are mentioned later.

TABLE 1.—*Antibacterial Action of Penicillin*

Susceptible Organisms	Insusceptible Organisms
Diplococcus pneumoniae	Eberthella typhosa
Streptococcus pyogenes	Salmonella paratyphi
Streptococcus salivarius	Salmonella enteritidis
Microaerophilic streptococci	Shigella dysenteriae
Staphylococcus aureus	Proteus vulgaris
Staphylococcus albus (some strains)	Pseudomonas aeruginosa (Bacillus pyocyaneus)
Neisseria gonorrhoeae	Pseudomonas fluorescens
Neisseria intracellularis	Serratia marcescens (Bacillus prodigiosus)
Actinomyces bovis	Klebsiella pneumoniae
Bacillus anthracis	Haemophilus influenzae
Bacillus subtilis	Escherichia coli
Clostridium botulinum	Staphylococcus albus (some strains)
Clostridium tetani	Micrococcus albus (some strains)
Clostridium perfringens (welchii)	Monilia albicans
Corynebacterium diphtheriae	Monilia candida
Vibrio comma	Monilia krusei
Micrococci	Blastomyces
Streptobacillus moniliformis	Mycobacterium tuberculosis
Borrelia novyi (spirochete of relapsing fever)	Streptococcus faecalis
Treponema pallidum	Brucella melitensis
Leptospira icterohaemorrhagiae	Plasmodium vivax
Spirillum minus	Toxoplasma
Psittacosis virus	
Ornithosis virus	

Intrathecal Instillation.—It will be evident, when diffusion of penicillin into the various tissues is considered, that in treatment of meningitis or infections involving the cerebrospinal structures it is essential to supplement systemic therapy by daily instillations of 10,000 to 20,000 Oxford units of penicillin into the spinal canal. This amount of penicillin usually is dissolved in 10 cc. of isotonic solution of sodium chloride. Both the sodium and the calcium salts of penicillin have proved satisfactory for this method of administration.

Subcutaneous Administration.—Penicillin may be administered intermittently or continuously by subcutaneous infusion. However, absorption of subcutaneous fluids is erratic and variable. Moreover, concentrated solutions of penicillin may be irritating when given subcutaneously. It appears, therefore, that the intravenous or intramuscular method of administration is preferable.

Intramuscular Administration.—Intermittent intramuscular administration of penicillin is a simple and practical method. Every three hours, 10,000 or 20,000 Oxford units, in 2 to 4 cc. of isotonic solution of sodium chloride is injected. A standard 20 gage intramuscular needle 2½ inches long is suitable. Local irritation may occur occasionally, and at least eight injections in twenty-four hours are required. The concentration of penicillin in the blood rises rather sharply during the first hour following intramuscular administration and then falls to a very low value during the hour before the next injection is made (fig. 1). Such rather sharp rises and falls of the concentration in the blood of any antibacterial agent are not, as a rule, desirable in the treatment of bacterial infections, particularly severe, overwhelming sepsis.

Intravenous Administration.—Penicillin disappears from the blood even faster after a single intravenous injection than after a single intramuscular injection. Further, intermittent intravenous injection requires eight separate venipunctures per day. This method has been used, however, in some instances with satisfactory results.

The continuous intravenous drip method of administering penicillin, which is used at the Mayo Clinic, has been described elsewhere.[6] The dose of penicillin given in twenty-four hours by this method has varied considerably with different investigators. For treatment of some types of infection, many investigators believe that administration of 200,000 to 300,000 Oxford units per day is necessary. We have used, as a rule, no more than 80,000 units per day and, in many instances, 40,000 units. When increased supplies of penicillin are available, the problem of dosage may become of less significance. In our early work with penicillin, low doses were employed to spread a small supply of penicillin as far as possible. If subsequent experience indicates that the hazard of delayed recurrence is increased by using low dosage, obviously the amounts used must be increased. We consider, however, that 100,000 units per day is probably the maximal amount of penicillin necessary for treatment of the infections most commonly encountered. Delayed recurrence, in the presence of metastatic lesions, may occur at times regardless of the amount of penicillin used.

Local venous irritation at the site of injection may attend use of the continuous drip method. It seems especially likely to occur with certain batches of penicillin which probably contain impurities. Careful inspection of the intravenous apparatus, and changing the site of injection at the first sign of irritation, usually are sufficient to cope with this difficulty. Although we have administered penicillin for as long as eight days through the same vein and at the same site of injection, often it is necessary to change the apparatus every few days. In our experience, venous irritation does not occur in more than 5 to 10 per cent of cases.

The continuous intravenous drip method is used by us almost entirely except when suitable veins are not available. Under these circumstances the intermittent intramuscular method is used. It is our impression that approximately twice as much penicillin is required for satisfactory intramuscular treatment as is required when the intravenous drip method is employed.

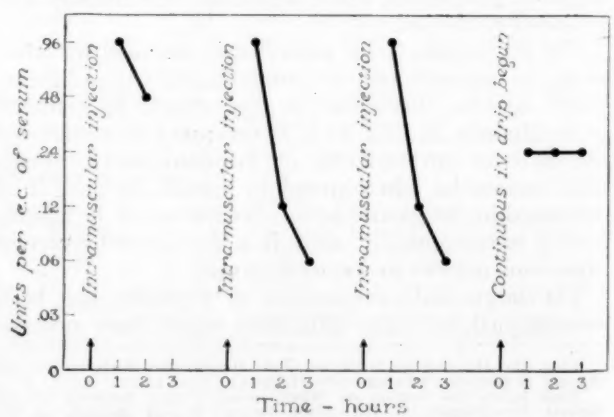

Fig. 1.—The falling serum concentration of penicillin in three hours when 50,000 units is administered by intramuscular injection and the approximately constant serum concentration when the same amount is given by continuous intravenous drip over the same period.

DIFFUSION OF PENICILLIN INTO VARIOUS TISSUES

Historical.—The test of the amount of active penicillin in the blood can be measured by the power of the blood serum to effect bacteriostasis. This is the test

6. Herrell, W. E.: The Clinical Use of Penicillin, an Antibacterial Agent of Biologic Origin, J. A. M. A. **124:** 622-627 (March 4) 1944.

which lies behind use herein of the terms "penicillin activity," "bacteriostatic activity," "concentration of penicillin" in the blood or in the tissue fluids, "blood level of penicillin," "penicillin content" and so on.

Florey and his associates [7] made the first report on distribution of penicillin in the body after it had been administered in different ways. From studies with experimental animals, they found that penicillin disappeared rather rapidly from the blood after a single intravenous injection but that a large percentage of the amount administered was found in the urine. When penicillin was given by subcutaneous injection, the concentration in the blood was less but a detectable amount was present for a longer period than after a single intravenous injection. Penicillin, when administered by any route, was found in a more concentrated form in the bile than in the blood serum, but the total amount excreted by the liver was small compared with that excreted by the kidneys. Penicillin was absorbed from the intestine when care was taken to protect the penicillin from being acted on by the acid of the stomach. Regardless of the method of administration, penicillin was found in the saliva in lower concentrations than in blood collected at the same time. Tears, pancreatic juice and spinal fluid had no antibacterial activity when penicillin was given intravenously. When a single intravenous injection of penicillin was given to human patients there was an initial high level of penicillin activity in the blood, followed by rapid loss of activity; large amounts of pencillin were excreted in the urine. When penicillin was introduced into the small intestine by means of a duodenal tube, the substance was found in the blood for a longer period than after a single intravenous injection. Penicillin also was detected in the blood after it had been given by mouth along with adequate amounts of sodium bicarbonate.

The Floreys,[8] reporting further clinical experiences with penicillin, included data on the presence of penicillin in the blood. Rammelkamp and Keefer [9] and Rammelkamp and Helm [10] extended to human patients the observations made by Florey and his co-workers on experimental animals. In addition, Rammelkamp and Keefer found that when penicillin was injected into inflamed body cavities such as a knee joint, a suprapatellar bursa or an empyema cavity, or when it was introduced into the cerebrospinal fluid, it could be detected in the blood and it was found to be present for as long as twenty-four hours in the region into which it had been injected. There was some evidence that penicillin passed more rapidly from the cerebrospinal fluid into the blood when the meninges were inflamed than when they were not.

Fleming [11] reported quantitative determinations of the bacteriostatic power of blood and cerebrospinal fluid of a patient with streptococcic meningitis who had been treated with penicillin. In another study Fleming [12] described a technic to determine the blood levels of penicillin that result from intravenous and intramuscular injection of different amounts of penicillin. He showed that the presence of leukocytes along with specific antibodies for the test organism added to the bacteriostatic power of the blood when penicillin was present. Thus he was able to explain why a favorable clinical result may occur even though penicillin cannot be detected in the blood by any of the methods available at present. Fleming also found that when penicillin was injected into an axillary abscess its presence could be detected in the abscess twenty-four hours later.

Present Work.—Since it has been demonstrated by others that intermittent intravenous injections of penicillin are not satisfactory for maintaining an adequate level of penicillin in the blood, further investigations were not made along this line. We were interested particularly in determining the penicillin activity of the blood of patients who were receiving penicillin by the continuous intravenous drip method, which has been used, for the most part, in our clinical studies. Using Fleming's adaptation of the Wright slide cell technic, determinations were made on one specimen from each of 11 patients who were receiving 40,000 units a day by continuous intravenous drip. The serum of 6 of these patients gave a value of 0.12 unit per cubic centimeter; in the serum of 1 was 0.06 unit per cubic centimeter, the serum of 2 contained 0.03 unit per cubic centimeter and there was no penicillin in the serum of 2 patients. The blood of 1 of these last 2 patients gave no evidence of activity on three different occasions. When this patient was given 100,000 units of penicillin a day by continuous intravenous administration, the amount of penicillin present in the blood serum was 0.12 Oxford unit per cubic centimeter. In the blood of another patient who was receiving 80,000 units a day by intravenous drip also there was 0.12 unit per cubic centimeter.

A study was made of the penicillin activity of the blood following intramuscular injections. Three patients were given 50,000 units of penicillin by intramuscular injection every three hours, and the bacteriostatic activity of the blood was determined at hourly intervals. The results are presented in figure 1. Even with the comparatively large amounts of penicillin administered, the blood taken one hour after injection did not contain more than 1 unit per cubic centimeter. Significant amounts of penicillin were detected in the blood throughout the period of treatment.

The amount of penicillin in the urine varied greatly with a number of factors. Some of the conditions influencing the results were the amount of penicillin administered, the volume of urine excreted and the presence or absence of bacteria in the urine. The presence of coliform bacteria was accompanied by rapid loss of penicillin activity when the specimen was kept at room temperature. On several occasions urine which contained coliform bacteria and in which the concentration of penicillin was high soon after being voided (as much as 120 units per cubic centimeter) completely lost its penicillin activity after being kept in the icebox overnight.

What is now to be said relates to an earlier paragraph on intrathecal instillation. The observation of Rammelkamp and Keefer that penicillin does not pass from the blood into the spinal fluid in detectable amounts was confirmed. Four persons were given 100,000 units of penicillin a day by continuous intravenous administration. Two specimens of cerebrospinal fluid were

7. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**: 177-188 (Aug. 16) 1941.
8. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**: 387-396 (March 27) 1943.
9. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425-437 (May) 1943. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342-350 (March) 1943.
10. Rammelkamp, C. H., and Helm, J. D.: Excretion of Penicillin in Bile, Proc. Soc. Exper. Biol. & Med. **54**: 31-34 (Oct.) 1943. Rammelkamp, C. H., and Helm, J. D.: Studies on the Absorption of Penicillin from the Stomach, ibid. **54**: 324-327 (Dec.) 1943.
11. Fleming, A.: Streptococcal Meningitis Treated with Penicillin: Measurement of Bacteriostatic Power of Blood and Cerebrospinal Fluid, Lancet **2**: 434-438 (Oct. 9) 1943.
12. Fleming, A., in discussion on Penicillin, Proc. Roy. Soc. Med. **37**: 101-104 (Jan.) 1944.

taken from each patient while this treatment was in progress but none gave evidence of penicillin activity. When 10,000 units of penicillin was administered intraspinally, penicillin activity could be detected in the spinal fluid twenty-four hours later. Values varied from a trace of penicillin to 0.06 unit per cubic centimeter.

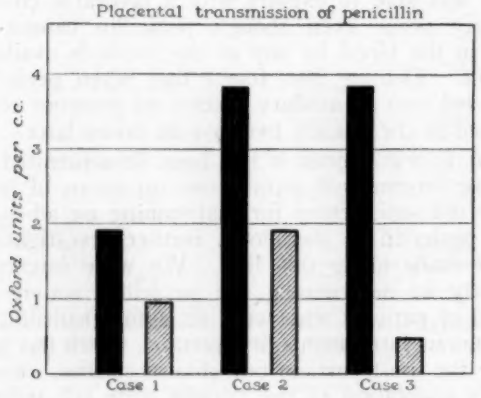

Fig. 2.—Columns represent penicillin found in blood: black columns, mother's blood; shaded columns, blood from umbilical cord. In the different cases 100,000 units of penicillin was administered at different intervals before delivery. In case 1 the interval was forty-five minutes, in case 2 fifteen minutes and in case 3 five minutes. In case 3 both mother's blood and blood from the umbilical cord gave positive complement fixation tests for syphilis.

Forty-eight hours after intraspinal administration of 10,000 to 20,000 units, no penicillin could be detected. Determinations were made three times on each of 3 patients.

In a consideration of the advisability of using penicillin in the treatment of antepartum syphilis, it is of importance to know to what extent penicillin given to the mother will pass into the placental circulation and become available to the fetus. Consequently, three observations were made on human subjects. A large amount of penicillin (100,000 units) was given during a relatively short time to each of 3 patients toward the end of the second stage of labor. At delivery, a short time later, a sample of blood from the umbilical cord and a sample of blood from the anterior cubital vein of the mother were obtained simultaneously. In 1 instance blood from the mother and that from the umbilical cord both gave positive serologic tests for syphilis. The results of these tests are presented in figure 2. It is evident from these studies that penicillin is transmitted through the placenta and is available to the fetus whether the pregnant mother is without evidence of disease or whether she has syphilis.

SUITABLE METHODS FOR DETERMINING THE PRESENCE OF PENICILLIN IN BODY FLUIDS

We have studied various methods described by others of determining the presence of penicillin in body fluids.[13] Also we have attempted to develop methods that would be more sensitive and more reliable than those used at present.

A number of determinations of penicillin activity were made on various body fluids, using both Fleming's method and that of Rammelkamp on the same specimens. The same amount of penicillin standard usually caused inhibition of bacterial growth in both tests, but there was often a difference between the two tests of one dilution in either direction. Tests of penicillin activity of blood serum and other body fluids frequently gave different results by the two methods.

In order to determine which method was more reliable, known amounts of penicillin were added to human serum in the laboratory of Dr. Fordyce Heilman and the mixtures were tested as unknowns by both methods. In preparing the samples, normal human serum was divided into five portions. To one portion was added 1 cc. of 0.85 per cent sodium chloride solution for each 4 cc. of serum. A similar proportion of 0.85 per cent sodium chloride solution was added to each of the other portions but, previous to the addition, a different amount of penicillin had been mixed with each quantity of sodium chloride solution and the actual concentration in each instance was recorded. Small amounts of each mixture were put into glass tubes, numbered by code and stored in carbon dioxide. A few tubes were taken at random each day for a period of several days to be tested as unknowns by one of us (D. H.). The standard used in the tests was the same preparation used in making the unknown serum-penicillin mixtures. The results of these experiments are presented in table 2.

Fleming's method was found to be reliable for determining the actual penicillin content of serum.[13a] The percentage of variation between the results obtained with the slide cell technic and the actual penicillin content did not exceed the 50 per cent variation that is to be expected when serial dilutions are employed. The presence of a large proportion of serum did not decrease the sensitivity of the test in detecting small amounts of penicillin. Fairly small amounts of penicillin (0.06 unit per cubic centimeter) were not detected by Rammelkamp's method and the results obtained were less uniform than those obtained with Fleming's test. In determining the penicillin content of the blood it is frequently desirable to be able to detect rather small amounts if they are present. It would seem that the Fleming test is superior in this respect to other quantitative methods available at present.

TABLE 2.—*Comparison of Fleming and Rammelkamp Methods Determining Penicillin Content of Serum*

Sample Number	Units per Cc. of Serum *	Fleming Method, Units per Cc.	Rammelkamp Method, Error, per Cent	Rammelkamp Method, Units per Cc.	Rammelkamp Method, Error, per Cent
1	4.00	3.84	4.0	3.84	4.0
2	0.06	0.06	0	0	...
3	0.06	0.06	0	0	...
4	4.00	3.84	4.0	3.84	4.0
5	1.30	0.96	26.2	0.96	26.2
6	1.30	0.96	26.2	0.96	26.2
7	0.06	0.06	0	0	....
8	1.30	0.96	26.2	0.96	26.2
9	1.30	0.96	26.2	0.96	26.2
10	0.25	0.24	4.0	0.12	52.0
11	0.25	0.24	4.0	0.12	52.0
12	0.06	0.06	0	0	....
13	0.06	0.06	0	0	....
14	4.00	3.84	4.0	7.68	92.0
15	4.00	3.84	4.0	7.68	92.0
16	0.25	0.24	4.0	0.24	4.0
17	0.25	0.24	4.0	0.24	4.0
18	0	0	0	0	0
19	0	0	0	0	0
20	0	0	0	0	0
21	0.25	0.24	4.0	0.24	4.0
22	1.30	1.92	47.7	1.92	47.7
23	4.00	3.84	4.0	7.68	92.0

* Samples were run as unknowns.

13. Rammelkamp, C. H.: A Method for Determining the Concentrations of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**: 95-97 (Oct.) 1942. Fleming, A.: In Vitro Tests of Penicillin Potency, Lancet **1**: 732-733 (June 20) 1942. Dawson, M. H.; Hobby, Gladys L.; Meyer, K., and Chaffee, Eleanor: Penicillin as a Chemotherapeutic Agent, Ann. Int. Med. **19**: 707-717 (Nov.) 1943. Dawson, M. H., and Hobby, Gladys L.: The Clinical Use of Penicillin: Observations in One Hundred Cases, J. A. M. A. **124**: 611-622 (March 4) 1944. Gardner, A. D.: Morphological Effects of Penicillin on Bacteria, Nature, London **146**: 837-838 (Dec. 28) 1940. Fleming, A.: Personal communication to the authors. Abraham, Chain, Fletcher, Gardner, Heatley, Jennings and Florey.[1] Fleming.[11]

13a. The details of the method will be published elsewhere.

Fleming's method has certain other advantages. It is not necessary to use sterile technic in performing the test and material to be tested does not have to be filtered to insure sterility if it is tested soon after it is received. When the slide cell method is performed with micropipets very small amounts of the fluid to be tested are necessary and but little equipment is needed. The end point is easily determined, and the entire test is complete in eighteen hours. In the Rammelkamp test it is recommended that some of the contents of a few tubes near the end point be cultured on blood agar to insure sterility. This requires an additional twenty-four hour period in order to complete the test.

ANALYSIS OF RESULTS IN 150 CASES

Including the first case reported from the Mayo Clinic in which penicillin was used,[14] we have employed penicillin in the treatment of 150 patients suffering from infections owing to a variety of pathogenic bacteria. The present report deals with the results in these cases. The sodium salt of penicillin was used in 103 of the 150 cases. Two of us (W. E. H. and D. R. N.[15]) have reported previously on the calcium salt of penicillin. We have found it entirely satisfactory for local, intravenous, intramuscular and intrathecal use. It can be kept at room temperature for long periods without evidence of loss of activity. In studies[16] of cytotoxicity carried out in our laboratories, several preparations of the calcium salt proved less toxic than samples of the sodium salt tested in a similar fashion. The calcium salt was used in 47 of the cases herein reported.

Bacteremia.—At the time of preparation of the present report we had used penicillin in 28 cases of bacteremia. One of these cases will be counted again among the cases of meningitis. The organism identified in 25 of these cases was Staphylococcus aureus. An anaerobic streptococcus was isolated in 1 case, hemolytic streptococci in 1 and Neisseria intracellularis in 1. The sodium salt of penicillin was used in 16 of the cases and the calcium salt in 12. Twenty-five of the 28 patients recovered satisfactorily (89 per cent). The 3 patients who failed to recover all died of acute vegetative endocarditis and all had presented suggestive evidence of endocarditis at the time penicillin therapy was started. With 1 or 2 exceptions, all of these 28 patients were given the daily dose of penicillin previously recommended by us. In only 1 instance was there evidence of a delayed metastatic lesion which might possibly have been associated with the use of inadequate amounts. This case will now be reported:

A woman aged 20 was admitted at the clinic five days after onset of her illness, which had followed self-inflicted trauma to a furuncle on the chin. Subsequent to this trauma, extensive cellulitis had involved the chin, face and neck. Her temperature suddenly had risen to 105 F. Blood taken by her local physician had revealed Staphylococcus aureus on culture. She had been treated intensively with sulfadiazine. In spite of this the cellulitis had progressed rapidly and blood cultures had remained positive.

At the time of the patient's admission, the blood culture revealed 10 colonies of Staphylococcus aureus per cubic centimeter. The woman was unable to open the mouth or to swallow. She received 60,000 units of the calcium salt of penicillin daily by the intravenous drip method for nine days (total 540,000 units). A blood culture obtained twenty-four hours after use of penicillin had been started revealed 1 colony of Staphylococcus aureus per cubic centimeter. Blood cultures taken forty-eight hour after administration of penicillin had been started were negative, and three subsequent cultures were also negative. The temperature reached normal on the sixth day and remained normal thereafter. There was regression of the edema of the soft parts, and ninety-six hours after treatment had been started the patient could open the mouth without difficulty and was able to take a normal diet (fig. 3 *a*, *b* and *c*). On the twelfth day after admission, the patient was dismissed from the hospital and returned to her home. She felt well and made no complaints.

Fig. 3.—*a*, appearance of patient at onset of penicillin therapy. Extensive cellulitis of mouth and face with extension into the cervical tissues. Staphylococcic septicemia. Patient gravely ill. *b*, appearance of patient seventy-two hours after treatment with penicillin was started. *c*, appearance of patient six days after penicillin therapy was started. Edema and cellulitis have practically disappeared. Complete recovery.

Several days after the woman had returned home, according to her account, she contracted a chest cold and a productive cough developed. She had a slight chill and a temperature of 103 F. and she also complained of pain in the left side of the thorax. She was treated with sulfamerazine by her local physician but, because of the persistence of her cough, she was readmitted at the clinic eighteen days after her dismissal. Blood cultures on readmission were negative. The bacteremia had not recurred nor was there any recurrence or difficulty with the initial lesion of the face. Roentgenograms of the thorax revealed a very small abscess in the upper lobe of the left lung. On this second admission the temperature was never higher than 98.6 F. Nevertheless, a second course of the calcium salt of penicillin was administered by the intravenous drip method. The patient received 80,000 units per day for seven days (total 560,000 units) and recovered.

The possibility of development of a delayed questionable metastatic lesion may argue in favor of higher doses. On the other hand, it would be interesting to

14. Herrell, W. E.; Heilman, Dorothy H., and Williams, H. L.: The Clinical Use of Penicillin, Proc. Staff Meet., Mayo Clin. **17**: 609-616 (Dec. 30) 1942.
15. Herrell, W. E., and Nichols, D. R.: The Calcium Salt of Penicillin, Proc. Staff Meet., Mayo Clin. **18**: 313-319 (Sept. 8) 1943.
16. Herrell, W. E.: The Role of Penicillin in the Treatment of Bacterial Infections, South. M. J. **37**: 150-156 (March) 1944. Herrell.[6] Herrell and Nichols.[15]

know the incidence of delayed recurrence in the presence of systemic infections of this type when even larger doses had been administered as a routine.

Subacute Bacterial Endocarditis.—Early in the course of our studies, penicillin was used in 4 cases of subacute bacterial endocarditis. In 2 of these cases a nonhemolytic streptococcus was the organism isolated, and in the other 2 cases a micrococcus was isolated. In all 4 cases treatment resulted in failure. The blood cultures in 1 of these cases became negative and remained negative for several months, but the patient died of heart failure. It seems apparent that the usual doses of penicillin are ineffective against subacute bacterial endocarditis. Recent reports from elsewhere, however, indicate that in early cases encouraging results have been obtained when 200,000 units or more of penicillin is given daily.

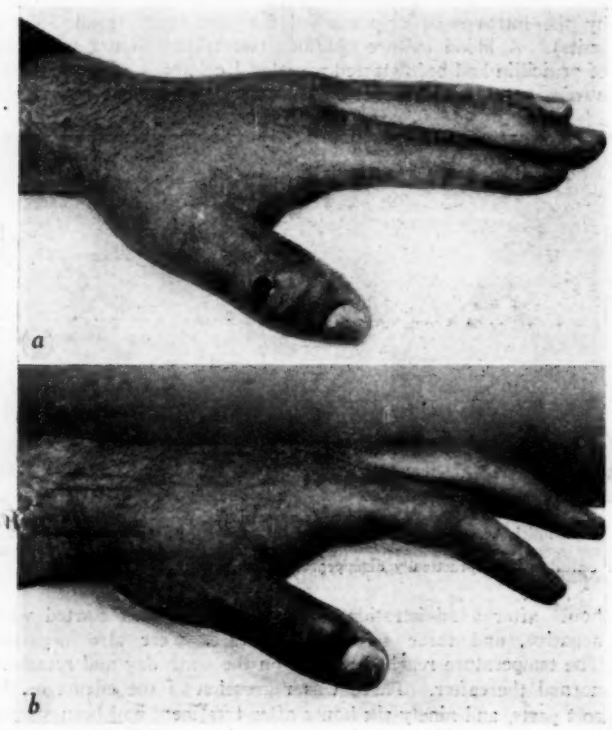

Fig. 4.—*a*, draining sinus of thumb associated with osteomyelitis of the interphalangeal joint; cultures positive for Neisseria gonorrhoeae. *b*, appearance of thumb after penicillin therapy. Sinus completely healed. No limitation of motion in joint.

Final evaluation of results in the treatment of subacute bacterial endocarditis will depend on further observations.

Severe Cellulitis Without Bacteremia.—Penicillin was used in 25 cases of severe cellulitis without bacteremia. Streptococcus pyogenes was the organism isolated in 13 cases. In 9 Staphylococcus aureus was the organism of infection. In 3 the infections were with mixed organisms, including anaerobic streptococci, green producing streptococci and Vincent's spirillum. The results were satisfactory in 22 of the 25 cases. Failures or doubtful results were obtained in 3.

Postoperative Wound Infection.—Penicillin has been used in the treatment of 8 very severe postoperative wound infections. In most instances the organism isolated from these wounds was Streptococcus pyogenes or Staphylococcus aureus. In 5 of these cases both organisms were present. The results were entirely satisfactory in 7 of the 8 cases.

Osteomyelitis.—Penicillin has been used alone or in combination with surgical measures in 22 cases of osteomyelitis. Since penicillin is active against most strains of Staphylococcus aureus as well as against the microaerophilic streptococci, it was reasonable to hope early in the course of studies on penicillin that it would prove effective in the treatment of osteomyelitis. Of the 22 cases of osteomyelitis, 11 were of the acute or subacute type. Of the 11, 9 were examples of spreading osteomyelitis of the maxillary or frontal bone, in which the organism isolated was the microaerophilic streptococcus. Penicillin, combined with surgical eradication of the diseased bone, yielded a satisfactory recovery in all 9 cases. There were 2 cases of acute fulminating osteomyelitis involving the long bones due to Staphylococcus aureus. Both patients recovered, although it was necessary to resort to surgical drainage in both cases. It may be possible that osteomyelitis of the flat bones responds more satisfactorily than osteomyelitis of the long bones.

In 11 cases of chronic osteomyelitis, penicillin has been used in treatment. The results are listed tentatively as doubtful in 10 and satisfactory in 1. Long observation must precede definite conclusions. In any event, it must be stated again that thorough surgical drainage and eradication of foci play important parts in the successful treatment of this disease.

Gas Gangrene.—Penicillin has been employed in treatment of 6 patients suffering with gas gangrene. Organisms predominantly present in these cases were Clostridium welchii and anaerobic streptococci. In 1 of the cases antitoxin was not used. In the remaining 5 cases antitoxin and, in some instances, surgical treatment were combined with penicillin. The results were satisfactory in 4, and failures occurred in 2 instances. We feel, as do the British investigators,[17] that antitoxin must be combined with penicillin. While penicillin may definitely inhibit the growth of the organisms associated with gas gangrene, the neutralizing effect of antitoxin is essential.

Sulfonamide Resistant Gonorrhea.—Since the first report[18] on experimental and clinical effectiveness of penicillin in sulfonamide resistant gonorrhea, penicillin has been found an exceedingly effective agent in treatment of this disease. Although we have treated a total of only 19 patients, all 19 have had satisfactory results. Two of these patients were suffering with gonorrheal arthritis in addition to sulfonamide resistant urethritis. The symptomatic response of the arthritis was striking. The arthritis was cured in both cases without instillation of penicillin into the joint. In 1 instance the arthritis involved the knee and in the other case the interphalangeal joint of the thumb. In this instance a draining sinus was present and cultures from this sinus revealed Neisseria gonorrhoeae. Roentgenograms revealed suppurative arthritis, with osteomyelitis. Without surgical intervention, complete healing resulted and roentgenograms after treatment were negative. This lesion, before and after treatment, is represented in figure 4 *a* and *b*. It is rarely necessary to use more than 100,000 to 150,000 units of penicillin as a total dose in the treatment of uncomplicated genitourinary neisserian infections. It may be necessary to use more in certain cases in which the condition is complicated by arthritis, endocarditis and so forth.

17. Discussion on Penicillin, Lancet **2**: 638-639 (Nov. 20) 1943.
18. Herrell, W. E.; Cook, E. N., and Thompson, Luther: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**: 289-292 (May 29) 1943.

Actinomycosis.—Twelve patients with maxillofacial, thoracic or abdominal actinomycosis have been treated with penicillin. In 2 cases the treatment is listed as having failed and in 2 as having given satisfactory results. The remaining 8 of the 12 patients have not been followed long enough to justify final statements as to the outcome, and for that reason results in these 8 cases are listed as doubtful. Before a final report on actinomycosis is submitted, it is planned to follow these patients for at least eighteen months. At that time a detailed report on sensitivity of the organism, methods of treatment and results will be made.

Infections of the Urinary Tract.—Infections of the urinary tract due to susceptible organisms, such as Staphylococcus aureus, respond satisfactorily to penicillin. Seven patients have been treated. In 4 cases the result can be considered entirely satisfactory. In 3 the result was doubtful or failure resulted because of the ineffectiveness of penicillin against gram-negative organisms such as Proteus, Pyocyaneus and Escherichia coli.

Meningitis.—Penicillin was used in treatment of 4 patients suffering with meningitis. Two of these cases were examples of meningitis due to Neisseria intracellularis, in 1 of which there was an accompanying bacteremia and in 1 of which there was not. The patient suffering with meningitis and bacteremia recovered; the other died. The infection of both patients had resisted sulfonamide therapy. Of the 2 other cases in which penicillin was used, 1 was an example of meningitis due to an anaerobic streptococcus. In this case the spinal fluid became negative under penicillin therapy and it appeared that the meningitis had responded satisfactorily. On the other hand, the patient died of an abscess of a frontal lobe of the brain. The fourth patient suffered with overwhelming meningitis due to staphylococci; the patient died. All these patients received, in addition to intravenous or intramuscular therapy, daily intrathecal injections of penicillin in the amounts outlined in the paragraph on intrathecal instillation.

Pulmonary Suppurative Disease.—Penicillin was used in the treatment of 6 patients suffering with pulmonary suppurative disease. Included in this group were pneumonia, pulmonary abscess and empyema. The results were satisfactory in 5 of the 6 cases. Failure occurred in the treatment of a man aged 66 who was suffering from extensive bilateral postoperative pneumonia due to Diplococcus pneumoniae, type III. In spite of intensive penicillin therapy, the patient died.

Miscellaneous Diseases.—Listed under miscellaneous diseases are 10 cases, in 6 of which satisfactory results were obtained. Of the 6 patients who obtained satisfactory results 4 had suppurative disease of the middle ear or mastoid process. Infection in all 4 had resisted sulfonamide therapy and all recovered. The organism isolated in 3 of the 4 cases was Staphylococcus aureus and, in 1, Streptococcus pyogenes was the infecting organism. Of the other 2 of the 6 cases in which the results were satisfactory 1 was an example of extensive ophthalmitis and conjunctivitis due to Neisseria intracellularis. In the other the organism isolated from the throat was Corynebacterium diphtheriae.

The 4 cases in the miscellaneous group in which failure occurred included 1 case of bilateral otitis media in which the infection was complicated by severe enteritis; the patient was an infant and the causative organism was the Staphylococcus aureus. One case represented severe brucellosis with brucella bacterial endocarditis. In 1 case acute leukemia was accompanied by secondary infection of the jaw, and the fourth failure occurred in a case in which penicillin was tried against induced malaria due to Plasmodium vivax. The results in the entire series are listed in table 3.

Comment on the Analysis of Cases.—It is evident from examination of the clinical results just reported that penicillin is an effective agent in treatment of practically all of the staphylococcic infections, whether or not bacteremia is present, with the possible exception of chronic osteomyelitis. These infections include extensive cellulitis, meningitis, pulmonary suppurative disease, suppurative disease of the kidney and infected wounds. Penicillin is equally effective against hemolytic streptococcus infections with or without bacteremia. It appears to be effective in the treatment of gas gangrene and anaerobic streptococcus infections. It is effective against sulfonamide resistant infections with Diplococcus pneumoniae and against all of the sulfonamide resistant gonorrheal infections, including complications commonly encountered in this disease.

TABLE 3.—*Results of Treatment with Penicillin in 150 Cases*

Clinical Diagnosis	Cases	Results		
		Satisfactory	Doubtful	Failure
Bacteremia	28	25	..	3
Subacute bacterial endocarditis	4	..	..	4
Severe cellulitis without bacteremia	25	22	1	2
Postoperative wound infection	8	7	..	1
Osteomyelitis				
Acute	11	11	..	..
Chronic	11	1	10	..
Gas gangrene	6	4	..	2
Sulfonamide resistant gonorrhea	19	19	..	..
Actinomycosis	12	2	8	2
Infection of urinary tract	7	4	1	2
Meningitis	4	1	..	3
Pulmonary suppurative disease	6	5	..	1
Miscellaneous diseases	10	6	..	4
Total	151*	107	20	24

* 151 diagnoses because of 1 patient who had both bacteremia and meningitis.

Further observation will be necessary; however, penicillin appears to be promising in the treatment of certain types of infections due to Actinomyces bovis. One of the most interesting observations in connection with studies on penicillin is that which concerns its antispirochetal action, first reported by Mahoney, Arnold and Harris.[19] Since the report by Mahoney and his associates,[19] F. R. Heilman and one of us [20] have found penicillin to be effective against other spirochetal infections, including relapsing fever and Weil's disease. Our experimental studies on relapsing fever have received confirmation in the reports by Lourie and Collier [21] and by Augustine, Weinman and McAllister.[22] It would appear from the studies of Lourie and Collier and from the studies reported by Heilman and one of us [23] that penicillin is also effective against Spirillum minus, one

19. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24:** 355-356 (Dec.) 1943; Am. J. Pub. Health **33:** 1387 (Dec.) 1943.

20. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Relapsing Fever, Proc. Staff Meet., Mayo Clin. **18:** 457-467 (Dec. 1) 1943; Penicillin in the Treatment of Experimental Leptospirosis Icterohemorrhagica (Weil's Disease), ibid. **19:** 89-99 (Feb. 23) 1944.

21. Lourie, E. M., and Collier, H. O. J.: The Therapeutic Action of Penicillin on Spirochaeta Recurrentis and Spirillum Minus in Mice, Ann. Trop. Med. **37:** 200-205 (Dec. 31) 1943.

22. Augustine, D. L.; Weinman, D., and McAllister, Joan: Rapid and Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in the Treatment of Trypanosomiasis (Trypanosoma Lewisi) and Toxoplasmosis, Science **99:** 19-20 (Jan. 7) 1944.

23. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Infections with Spirillum Minus and Streptobacillus Moniliformis (Rat Bite Fever), Proc. Staff Meet., Mayo Clin. **19:** 257-264 (May 17) 1944.

of the etiologic organisms of rat bite fever. Clinical studies have not as yet been reported on the spirochetal diseases which we have studied in experimental animals. Evidence is accumulating that penicillin has a definite place in syphilotherapy.

CONTRAINDICATIONS TO PENICILLIN THERAPY

On the basis of present knowledge, use of penicillin should not be attempted in treatment of gram-negative bacillary infections such as undulant fever, tularemia or influenza, or in the treatment of infections due to the colon-typhoid-dysentery group of organisms or to Friedländers' bacillus. Infections of the urinary tract due to the gram-negative organisms mentioned do not respond to penicillin therapy. At present it appears that penicillin should not be employed in the treatment of tuberculosis, acute rheumatic fever, lupus erythematosus, pemphigus, mononucleosis, leukemia, ulcerative colitis, malaria, blastomycosis and certain virus infections. On the other hand, the experimental work of F. R. Heilman and one of us [24] strongly suggests that penicillin may prove of value in the treatment of at least two virus infections in man; namely, ornithosis and psittacosis.

REACTIONS

Clinical experience with penicillin indicates that its use is not attended by many serious toxic reactions. There has been no evidence of disturbance in the peripheral blood or in the hemopoietic system. On the contrary, penicillin can be successfully used in the presence of pronounced anemia or pronounced leukopenia or even complete agranulocytosis. We have repeatedly seen suppressed leukocyte counts rise during the course of penicillin therapy in the face of overwhelming infection associated with suppression of the bone marrow. No evidence of renal toxicity has been seen.

The local irritation at the site of intramuscular and intravenous injection of penicillin already has been dealt with.

As long as pyrogen free penicillin is used, febrile reactions are not likely to occur. Cutaneous sensitivity to penicillin itself, or perhaps to impurities in the preparations, has been observed in only 2 of 150 cases. In both instances the reaction occurred when penicillin from one commercial source was being administered. When urticaria or dermatitis develops as the result of sensitivity to penicillin, great caution must be used in continuing to administer the material. Persistence of treatment in the face of a generalized cutaneous reaction might lead to development of exfoliative dermatitis. The skin of many persons is known to be sensitive to various molds and mold products. This cutaneous toxic reaction may become of more significance as penicillin is more generally used.

SUMMARY AND CONCLUSIONS

Penicillin therapy should be confined to infections due to pathogens known to be susceptible to its action.

Serious toxic reactions have not followed use of either the sodium or the calcium salt for intrathoracic, intra-articular or intrathecal instillation; nor have such reactions attended local application or intramuscular or intravenous administration in the doses recommended.

Local irritation at the site of injection of either the sodium or the calcium salt of penicillin varies with different batches. Changing the site of administration or changing the product often will terminate this reaction. The only other toxic reaction of any significance is the occurrence of urticaria and irritative dermatitis. The latter reaction is very infrequently seen. Febrile reactions may occur if the penicillin employed is not pyrogen free.

The continuous intravenous drip method of administration of penicillin best maintains a constant level in the blood.

While penicillin diffuses fairly readily into most tissues, it does not reach the spinal fluid following intravenous or intramuscular injection. It is necessary, therefore, to administer penicillin by the intrathecal route at least once daily in treatment of infections involving the cerebrospinal structures. Following intravenous administration of penicillin, antibacterial amounts of the material reach the fluid of septic joints. Likewise, penicillin is transmitted through the placenta from the mother to the fetus. This is important in penicillin therapy for antepartum syphilis.

We believe Fleming's adaptation of the Wright slide cell technic to be the most reliable method of determining the penicillin content of serum.

Of 150 patients suffering with infections owing to a variety of pathogenic bacteria, 103 were treated with the sodium salt of penicillin and 47 with the calcium salt. The calcium salt is handled more easily and appears more stable. Among 28 patients suffering with bacteremia, most of whom had resisted sulfonamide therapy, 25 recovered and 3 died. At present, 80,000 units in twenty-four hours appears to be the most satisfactory dose in cases of bacteremia.

Other bacterial infections for which we have used penicillin include bacterial endocarditis, severe cellulitis, postoperative wound infection, osteomyelitis (acute and chronic), gas gangrene, sulfonamide resistant gonorrhea, actinomycosis, infections of the urinary tract, meningitis, pulmonary suppurative disease and a small group of miscellaneous infections. The results with 107 patients (1 of whom was counted twice, as is explained in table 3) could be considered brilliant or satisfactory; doubtful results or failures occurred with 44.

The use of penicillin should not be attempted in the treatment of gram-negative bacillary infections, including undulant fever, tularemia, influenza, infections due to the colon-typhoid-dysentery group or infections due to Klebsiella pneumoniae. Infections of the urinary tract due to gram-negative organisms do not respond to penicillin. It has not proved useful in treatment of tuberculosis, acute rheumatic fever, lupus erythematosus, pemphigus, mononucleosis, leukemia, ulcerative colitis, malaria or blastomycosis.

ABSTRACT OF DISCUSSION

DR. WALTER S. PRIEST, Chicago: I concur that the constant intravenous drip is the method of choice whenever feasible. It is possible to give the intravenous drip as slowly as 8 to 12 drops per minute continuously over periods of days without removing the needle, and that enables one to keep down the fluid intake where that is necessary. I have not been as fortunate as Dr. Herrell in regard to venous irritation, but I find, as he does, that it is not significant and that permanent thrombophlebitis has been a rarity. The reaction subsides promptly. Regarding the intramuscular administration, I have had one experience in which the patient had less irritation by using a more concentrated solution, up to 15 or 16 thousand units per cubic centimeter instead of the more usual 5 thousand. Dr. Herrell's comments on the use of 80 thousand units for twenty-four hours are noteworthy. Perhaps I have fallen into the habit of using larger doses unnecessarily. Since the present ampules are put

24. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Ornithosis, Proc. Staff Meet., Mayo Clin. **19**: 57-65 (Feb. 9) 1944; Penicillin in the Treatment of Experimental Psittacosis, ibid. **19**: 204-207 (April 19) 1944.

up with a hundred thousand units per cubic centimeter it may be more practical to start with that as the initial twenty-four hour dose, by whatever method given, giving a somewhat larger dose at first and then adjusting the dose up or down as the patient's reaction seems to warrant. Certainly the smallest dose necessary to get the result is the one which should be used. During the past year I have had an opportunity to study the use of penicillin in large doses in 8 cases of subacute bacterial endocarditis. The infective organisms were of the viridans group, the hemolytic streptococcus group and the nonhemolytic nonrenal recrudescent streptococci. These patients received from 100 thousand to 400 thousand units of penicillin in twenty-four hours by the continuous intravenous drip method over a period of not less than four weeks. Out of this group, 2 are apparently cured, 1 is fever and bacteria free but still with an elevated sedimentation rate, 2 appear to be frank failures but are still alive, and 3 have died during the course of treatment. Has Dr. Herrell had any experience in the treatment of bronchiectasis with pencillin?

DR. K. R. BROWN, Des Moines, Iowa: I want to know whether Dr. Herrell finds penicillin effective in cavernous sinus thrombosis complications from facial cellulitis.

DR. WINGATE M. JOHNSON, Winston-Salem, N. C.: Dr. Herrell gave an exhaustive list of diseases in which penicillin is indicated and in which it is not. I don't believe he mentioned one important group, the rickettsial diseases.

DR. WALLACE E. HERRELL, Rochester, Minn.: The point which Dr. Priest raised as to whether or not higher concentrations might have prevented the three failures in the cases of bacteremia deserves consideration. We find that administration of 80 thousand units in twenty-four hours results in a concentration of penicillin which is adequate to inhibit the organisms. Since most of the penicillin is dispensed in ampules of 100 thousand units I am inclined to agree that in general practice it would probably be worth while to use the contents of the 100 thousand unit ampule in preparing the twenty-four hour dose. Excluding bacterial endocarditis, however, we still do not feel that 200 to 300 thousand units per day is necessary to obtain satisfactory results in cases of bacteremia when the agent is administered by the intravenous drip method. The penicillin content of the blood of a patient receiving around 80 thousand units per day will usually be found to be somewhere around 0.06 to 0.12 Oxford unit per cubic centimeter, which is adequate to cause complete inhibition and keep the blood sterilized. In the 3 individuals who failed to recover, necropsy revealed acute ulcerative endocarditis. All 3 had heart murmurs and other clinical signs suggestive of endocarditis at the time penicillin therapy was started. When endocarditis is present at the time one begins penicillin therapy, the results usually will not be satisfactory even when very large amounts of penicillin are administered; at least this has been our experience. Better results will be obtained in the treatment of patients with bacteremia when it is no longer necessary to defer penicillin therapy until sulfonamides have been tried and have failed. I am sure Dr. Priest feels that it is too early to evaluate these results completely, but it is well worth while to continue to treat these patients so long as the organism present in their blood is found to be sensitive to penicillin. Many of the organisms present in subacute bacterial endocarditis are not sensitive. Dr. Priest's remarks concerning the febrile reactions incident to intravenous therapy are extremely important. Old tubing and apparatus not carefully prepared will result in febrile reactions which are not truly due to the penicillin. One must use the same precautions that he would in any intravenous medication. The same precautions must also be rigidly observed when penicillin is given intramuscularly, to avoid the introduction of bacteria or foreign substances which might lead to the development of localized abscesses. It is well known that patients receiving penicillin intramuscularly eight times a day are liable to get "needle shy." We have not had any experience in the treatment of bronchiectasis per se, although we have used penicillin therapy with encouraging results in preparation for lobectomy and in postoperative treatment. Concerning sinus thrombosis, it is safe to say that penicillin has resulted in a cure in many cases. I feel certain that 1 of our patients suffering from staphylococcic bacteremia had a sinus thrombosis and that he recovered as a result of penicillin therapy. This particular patient never regained vision in one eye. Concerning the effectiveness of penicillin against rickettsial infections, I might call attention to the experimental work reported by Pinkerton and his associates of St. Louis, which indicates that penicillin may prove effective against experimental typhus. Enough data have not yet been accumulated to warrant any statements concerning the clinical use of penicillin in virus infections. A virus may be quite susceptible to the action of penicillin and one may still not obtain a satisfactory clinical result, especially if the virus has become well fixed in the cells by the time one gets an opportunity to treat the patient.

PENICILLIN IN THE TREATMENT OF MENINGITIS

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Reports in the literature pertaining to the clinical effects of penicillin in the treatment of meningitis have in general been confined to observations on small groups of patients or on isolated cases.[1] No definite conclusions may be drawn from them concerning the efficacy of penicillin, the most satisfactory method of treatment or the minimum adequate dosage requirements. However, from in vitro studies demonstrating the pronounced sensitivity of the meningococcus, Streptococcus haemolyticus, pneumococcus and some strains of Streptococcus viridans to the action of penicillin, this agent should prove to be of considerable therapeutic value in the management of such infections, particularly in individuals who are sulfonamide resistant or sulfonamide reactors.

In a preliminary report [2] on 31 patients with cerebrospinal fever, we recorded 30 recoveries following the combined intrathecal and intravenous or intramuscular use of penicillin and concluded that penicillin is a safe, effective and highly potent agent in the treatment of this disease. Since then we have treated 40 additional patients with meningitis without a fatality. We are presenting at this time a report of our observations on this entire group of 71 patients.

MATERIAL

Cerebrospinal Fever.—Sixty-five patients in this series presented clinical evidence of cerebrospinal fever (table 1). In almost all patients the onset was sudden, with rapidly developing headache, nausea, vomiting and cervical rigidity of eight to forty-eight hours' duration. Twenty-four patients were semicomatose and 21 were comatose. The temperature on admission ranged between 99 (rectal) and 108 F. (rectal); the average for the group was 102.7 F. (rectal). Petechiae were found in 48 instances, and in 4 of these a purpuric rash was also noted. One patient with most extensive

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1. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections, J. A. M. A. **122**: 1217 (Aug. 28) 1943. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, ibid. **123**: 1007 (Dec. 18) 1943. Dawson, M. H., and Hobby, G. L.: The Clinical Use of Penicillin: Observations in 100 Cases, ibid. **124**: 611 (March 4) 1944.

2. Rosenberg, D. H., and Arling, P. A.: The Treatment of Cerebrospinal Fever with Penicillin: A Preliminary Report, U. S. Nav. M. Bull., August 1944.

purpura presented the clinical picture of the so-called Waterhouse-Friderichsen syndrome. Two other patients who went into shock shortly after admission exhibited widespread petechial eruptions without purpura. Acute arthritis was observed in 15 of the patients on admission. The spinal fluid was turbid in all except 4 patients, and the initial spinal fluid cell count ranged from 21 to 50,100 leukocytes per cubic millimeter. The average cell count for the group was 11,700 per cubic millimeter, 88 per cent being polymorphonuclear leukocytes. In 49 patients meningococci were recovered from the spinal fluid, and in 10 of these the blood cultures were positive. In another patient with clinical evidence of fulminating meningococcemia the blood culture was positive although the spinal fluid was sterile and contained only 66 leukocytes per cubic millimeter. In the 3 other patients with clear spinal fluid on admission, meningococci were found in the spinal fluid on culture. Owing to a lack of serums we were unable to determine the type of meningococci isolated from this group of patients. In 15 patients the clinical picture and spinal fluid findings were characteristic of meningococcic meningitis, but the stained smears and cultures of the spinal fluid revealed no organisms.

Meningitis Due to Other Bacteria.—In 3 patients hemolytic streptococci were recovered from the spinal fluid (table 2). In one of these a bacteremia was present, and in another bilateral acute otitis media was found. Two of these patients were semicomatose on admission. The spinal fluid cell counts ranged between 1,000 and 2,290 leukocytes per cubic millimeter.

There were 2 patients with Streptococcus viridans bacteremia and meningitis, both of whom were comatose on admission. Although the initial spinal fluid cell count was 450 leukocytes per cubic millimeter in each instance, in 1 it rose to 25,600 within ten hours.

TABLE 1.—*Cerebrospinal Fever*

								Spinal Fluid			Penicillin (Units)		
Patient	Age	Duration	Coma	Semi-coma	Petechiae	Temperature	Blood Culture	Culture	Cell Count	Per Cent Polymorphonuclears	Intrathecal	Intravenous and/or Muscular	Complications
1	18	25 hr.	+	—	3+	104	0	+	50,100	98	125,000	860,000	
2	18	24 hr.	+	—	3+	104.8	0	+	15,000	92	100,000	900,000	Polyarthritis; thrombophlebitis
3	25	2 days	—	—	3+	101.6	0	+	8,000	98	45,000	340,000	
4	19	?	+	—	4+	108	+	+	7,200	90	55,000	380,000	Hydrocephalus; circulatory failure (autopsy)
5	23	26 hr.	+	—	3+	103.8	0	0	19,800	98	15,000	400,000	
6	20	1 day	—	—	1+	100.8	0	+	17,500	90	25,000	715,000	Fibrinous pericarditis; arthritis
7	69	2 days	—	+	0	104.2	0	0	8,600	89	25,000	280,000	
8	18	1½ days	—	+	3+	100.2	0	+	4,800*	75	15,000	260,000	
9	21	43 hr.	—	—	1+	102.4	0	+	11,100	100	10,000	235,000	
10	18	1½ days	—	—	0	101.4	0	0	12,800	92	10,000	180,000	
11	18	5 days	—	—	0	104	0	0	1,500	90	10,000	80,000	
12	20	48 hr.	—	+	2+	99.8	0	0	10,100	94	10,000	110,000	Transient diplopia, 4th day
13	18	29 hr.	+	—	1+	105	0	+	10,400	90	10,000	60,000	Acute otitis media, 3d day
14	18	17 hr.	+	—	0	102.4	+	+	21,000	94	10,000	40,000	Acute tonsillitis
15	20	2½ days	—	+	0	104.8	0	0	3,800	70	10,000	20,000	
16	18	3½ days	—	+	0	105	0	+	11,500	85	30,000	40,000	Sixth nerve palsy and paresis
17	19	1 day	+	—	3+	105.6	0	+	5,000	100	10,000	40,000	Epididymitis; arthritis
18	28	12 hr.	—	+	2+	103	0	0	6,600	89	10,000	20,000	
19	17	30 hr.	+	—	2+	102	0	+	17,300	99	50,000	290,000	Polyarthritis
20	18	21 hr.	—	—	0	99.8	+	+	14,100	96	30,000	40,000	
21	24	20 hr.	—	—	4+	103.8	+	0	66	94	None	250,000	Waterhouse-Friderichsen syndrome
22	29	40 hr.	—	+	1+	105.2	0	0	5,100	90	10,000	40,000	
23	27	34 hr.	—	+	2+	103.4	0	+	23,500	99	20,000	90,000	Epididymo-orchitis; diplopia
24	20	40 hr.	+	—	3+	105	+	+	13,100	93	10,000	90,000	Epididymo-orchitis; arthritis; diplopia
25	18	24 hr.	—	+	2+	103.2	0	+	14,800	92	20,000	90,000	
26	20	26 hr.	—	+	1+	101	0	+	11,400	95	30,000	115,000	
27	19	22 hr.	+	—	2+	105.2	0	+	18,700	100	20,000	155,000	
28	18	2 days	—	—	1+	104.2	0	0	6,000	92	10,000	100,000	Arthritis; acute tonsillitis
29	18	7½ hr.	+	—	0	104.8	0	+	18,700	93	10,000	100,000	
30	19	15 hr.	+	—	1+	102.4	0	0	8,100	94	10,000	90,000	Polyarthritis
31	18	1 day	+	—	3+	104.8	0	+	12,600	89	40,000	200,000	Epididymitis; polyarthritis
32	19	1 day	+	—	1+	103.8	0	0	12,100	100	10,000	70,000	
33	29	24 hr.	+	—	3+	103.6	+	+	22,500	96	30,000	70,000	Sixth nerve paresis
34	17	10 hr.	—	+	4+	102	+	+	2,000	100	50,000	250,000	Polyarthritis
35	18	15 hr.	—	+	2+	105.2	0	+	12,100	94	10,000	140,000	Polyarthritis
36	19	2 days	—	—	1+	102.6	0	0	6,200	68	10,000	40,000	
37	18	12 hr.	—	+	1+	104	0	+	2,500*	91	10,000	100,000	
38	22	2½ days	+	—	0	101.6	0	+	31,000	95	40,000	170,000	Thrombophlebitis
39	18	24 hr.	—	—	3+	101	0	+	4,200	90	20,000	100,000	Acute tonsillitis
40	20	16 hr.	—	+	3+	101	0	+	12,500	91	20,000	100,000	
41	17	7 hr.	+	—	0	103	0	+	10,800	99	20,000	100,000	
42	18	43 hr.	—	+	0	103.6	0	+	12,200	96	20,000	50,000	
43	18	46 hr.	—	—	1+	101.8	0	0	8,600	63	10,000	40,000	
44	18	4 days	—	+	4+	103.8	0	+	6,400	90	30,000	50,000	
45	32	1 day	+	—	2+	99.4	+	+	8,620	98	30,000	50,000	Epididymo-orchitis; arthritis
46	18	1 day	—	—	4+	102.2	0	+	7,900	94	20,000	100,000	Epididymitis, bilateral
47	35	17 hr.	—	+	4+	100.4	+	+	280	96	50,000	200,000	
48	26	2 days	—	+	4+	100.2	+	+	24,100	80	40,000	200,000	
49	18	1 day	—	—	3+	102	0	+	11,650	92	20,000	200,000	
50	21	1 day	+	—	0	102.6	0	+	21,600	96	20,000	200,000	Epididymitis
51	18	1 day	+	—	3+	100.6	0	+	12,700	97	20,000	200,000	
52	18	3 days	—	+	0	102	0	+	11,400	96	20,000	200,000	
53	18	1 day	—	+	1+	102.6	0	+	12,200	95	30,000	200,000	
54	18	4 days	—	—	0	100.8	0	+	9,300*	90	30,000	200,000	Acute tonsillitis
55	18	2 days	—	—	1+	101.8	0	0	9,200	95	10,000	200,000	
56	18	19 hr.	—	—	1+	102.6	0	+	3,200	98	30,000	335,000	Polyarthritis
57	18	15 hr.	—	+	1+	104	0	+	11,300	97	20,000	70,000	
58	18	8 hr.	—	—	0	103.6	0	+	255	88	10,000	None	
59	29	1 day	+	—	2+	99.8	0	+	20,400	100	50,000	50,000	Polyarthritis
60	18	2 days	—	—	0	102	+	+	2,600	96	20,000	50,000	
61	21	1 day	—	—	3+	100.2	0	+	21	0	20,000	230,000	Epididymo-orchitis; arthritis
62	25	1 day	—	+	3+	99	0	+	10,100	92	50,000	55,000	Arthritis; epididymitis
63	18	1 day	—	+	0	100.2	0	0	2,900	96	10,000	50,000	
64	27	12 hr.	—	+	2+	103.6	0	+	6,000	87	20,000	40,000	Epididymo-orchitis
65	23	2 days	—	—	1+	99	0	+	47,100	96	40,000	60,000	

* Cell count inaccurate owing to pellicle formation. In all cases the temperature was taken rectally. All patients were males.

In 1 patient with acute otitis media complicated by meningitis, pneumococci were cultivated from the spinal fluid. This patient was semicomatose on admission and the maximum temperature was 105.2 F. (rectal). The initial spinal fluid cell count was 1,100 leukocytes per cubic millimeter.

METHOD OF TREATMENT

Rammelkamp and Keefer [3] have demonstrated that penicillin administered intravenously does not appear in the spinal fluid. Injected intrathecally,[4] penicillin is slowly absorbed from the subarachnoid space and may be detected in the spinal fluid thirty-one hours later. It is more rapidly absorbed from the spinal fluid of patients with meningitis but may be found in significant amounts twenty-four hours after injection.

For purposes of investigation our plan of treatment varied somewhat in different patients, particularly from the standpoint of dosage. The most satisfactory method of treatment was found to be the following:

1. The initial diagnostic lumbar puncture was performed in the usual manner and the spinal canal was drained. Ten thousand Oxford units of sodium penicillin, dissolved in 10 cc. of isotonic solution of sodium chloride, was slowly introduced into the subarachnoid space. Penicillin (10,000 units) was administered intrathecally at twenty-four hour intervals until clinical improvement, sustained fall in temperature and/or a decrease in the meningeal signs were manifest and until the stained smears and cultures of the spinal fluid revealed no organisms. As penicillin was injected intrathecally with each lumbar puncture without awaiting the results of the bacteriologic studies, this plan in effect was tantamount to administering an additional dose of penicillin after the spinal fluid became sterile. We felt that in some instances it was unsafe to withhold treatment pending the results of the spinal fluid cultures. The persistence of coma was regarded as an indication for further intrathecal therapy. In the most severe infections and in those in which coma lasted forty-eight hours or longer, intrathecal penicillin was continued until the spinal fluid was bacteria free on three successive days. It is of paramount importance to drain the spinal canal as completely as is feasible before injecting penicillin. In several instances the spinal fluid was so viscous that aspiration was necessary.

2. Penicillin was also administered either by the continuous intravenous drip method at the rate of 5,000 units per hour or intramuscularly in doses of 15,000 units every three hours, the dose being reduced to 10,000 units every three hours if improvement was satisfactory. Generally, penicillin was given intravenously (40 units per cubic centimeter in a 5 per cent dextrose solution) for the first eight hours and continued intramuscularly thereafter. Patients with the fulminating type of cerebrospinal fever received penicillin intravenously at the rate of 10,000 units per hour for four hours initially. Owing to a lack of technical facilities the treatment could not be controlled by determinations of the amount of penicillin in the blood and spinal fluid. Instead, frequent clinical observations were made and the temperature, pulse and respirations were recorded every two hours.

In addition to specific therapy, 3,000 cc. of fluid was given daily. To combat shock in patients with fulminating meningococcemia, supportive therapy was given in the form of whole blood, plasma, epinephrine and desoxycorticosterone acetate. Oxygen therapy was employed when indicated.

TABLE 2.—*Meningitis Due to Other Bacteria*

Patient	Age	Duration	Coma	Semi-coma	Temperature	Blood Culture	Spinal Fluid: Culture	Spinal Fluid: Cell Count	Spinal Fluid: Per Cent Polymorphonuclears	Penicillin (Units): Intrathecal	Penicillin (Units): Intravenous and/or Muscular	Complications
						A. Streptococcus Haemolyticus						
66	27	8 days	—	+	103.8	+	+	2,300	93	20,000	400,000	
67	27	22 hr.	—	—	104.4	0	+	1,700	79	20,000	170,000	
68	25	4 days	—	+	101.4	0	+	1,000	85	20,000	650,000	Bilateral acute otitis media
						B. Streptococcus Viridans						
69	18	3½ days	+	—	104.6	+	+	450 25,600	85 95	40,000	300,000	Acute pharyngitis
70	24	3 days	+	—	102	+	0	450	97	30,000	200,000	
						C. Pneumococcus						
71	35	4 days	—	+	102	0	+	1,100	84	30,000	800,000	Acute otitis media

In all cases the temperature was taken rectally. All patients were males.

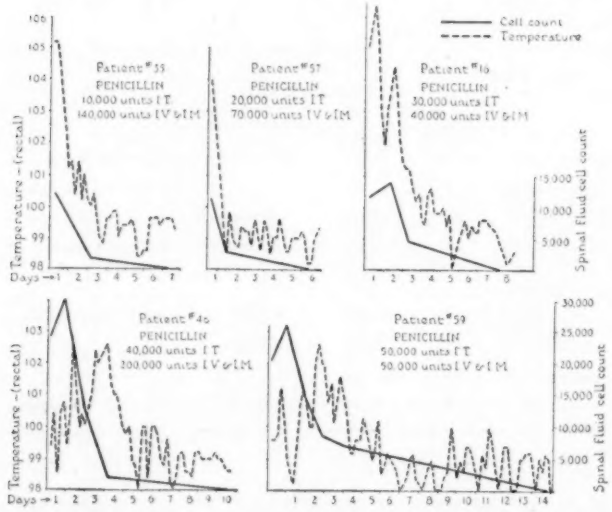
RESULTS

Cerebrospinal Fever.—Sixty-four of the sixty-five patients in this group recovered. The one fatality occurred in a patient who was admitted in a moribund state with clinical and bacteriologic evidence of meningococcemia and with well advanced meningitis. His temperature was 108 F., pulse rate 140 and respiratory rate 66 per minute. He received 12 Gm. of sodium sulfadiazine parenterally in addition to 55,000 units of penicillin intrathecally and 380,000 units intravenously and intramuscularly but died thirty-eight hours after admission. Necropsy disclosed suppurative meningitis, secondary hydrocephalus and edema of the brain and lungs.

In the 64 patients who recovered, progressive improvement was noted soon after penicillin therapy was begun and was generally signalized by the disappearance of the restlessness, stupor and delirium, cessation of vomiting and an abrupt fall in the temperature and pulse rate. Those who were comatose usually regained consciousness within two to twenty-four hours, but in 5 coma persisted for thirty to forty-eight hours and in 1 for four days. In 22 patients the temperature returned to normal within eight to

3. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Distribution of Penicillin, J. Clin. Investigation **22**: 425 (May) 1943.
4. Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection, Am. J. M. Sc. **205**: 342 (March) 1943.

seventy-two hours. In 16 a low grade intermittent fever (100 to 100.2 F. rectal) remained until the seventh day. In some of the latter patients as well as in those who exhibited a more prolonged febrile course the fever was found to be caused by one or more complications rather than by the meningitis, for the spinal fluid had become sterile and either gave a normal cell count or showed a residual lymphocytosis. Of the 4 patients whose temperature did not fall abruptly, 3 represented very severe infections and 1 showed signs of acute pericarditis and polyarthritis. Headache disappeared within two to four days and the signs of meningitis subsided completely in two to seven days (average, four days) except in our first 2 patients, who received 100,000 to 125,000 units intrathecally. In the latter the meningeal signs persisted for nine days. Generally there was a prompt reduction in the spinal fluid cell count, as shown in the accompanying chart, and the protein and sugar returned to normal rapidly. In all but the most severe infections this was accompanied by a disappearance of the polymorphonuclear leukocytes within four to seven days. In many a slight



Effect of penicillin on the temperature and spinal fluid cell counts of patients with cerebrospinal fever treated with 10,000, 20,000, 30,000, 40,000 and 50,000 units (total) intrathecally and various amounts intravenously and intramuscularly. Cases representing different grades of severity were selected. In patient 59, fever was prolonged by the presence of arthritis. The increase in the spinal fluid cell count in patients 16, 48 and 49 following the first injection of penicillin intrathecally was noted in 8 other patients. I. T., intrathecal; I. V., intravenous; I. M., intramuscular.

lymphocytosis remained until the tenth to the fourteenth day. In a few of our first patients a recurrence of fever was observed on the fourth to the sixth day if intrathecal penicillin was discontinued too soon. This was controlled by an additional dose of penicillin. As a rule the patients were able to be out of bed on the eighth day unless prevented by complications.

The amount of penicillin administered intrathecally to these patients varied with the severity of the meningeal infection. Thus, 42 patients recovered following only one or two injections of penicillin, 10 required three injections and 9 received four to five injections intrathecally. Through a lack of knowledge of the potency and effectiveness of penicillin, the first 2 patients whom we treated received nine and eleven injections respectively, totaling 100,000 to 125,000 units. Another patient with fulminating meningococcemia recovered with intravenous and intramuscular therapy alone, but in this instance the spinal fluid was sterile and showed only 66 leukocytes per cubic millimeter. The first 8 patients whom we treated received an intrathecal dose of 15,000 units dissolved in 15 cc. of isotonic solution of sodium chloride initially, but in view of the symptoms and signs of meningeal irritation resulting therefrom the 10,000 unit dose was employed thereafter. It is noteworthy that the amount of intrathecal penicillin necessary for recovery cannot be correlated with the initial spinal fluid cell count. Instead, it seems to depend on the number, type and virulence of the organisms as well as on the immunologic reaction of the host.

An analysis of the bacteriologic effects of penicillin on the spinal fluid obtained twenty-four hours after an intrathecal injection discloses that of 48 patients with positive cultures on admission in 29 the spinal fluid was sterile after one injection of penicillin, in 8 after two injections, in 3 after three injections and in 4 after four injections. However, in 2 others, both with very severe infections, the spinal fluid was sterile after one injection of penicillin but again showed meningococci twenty-four hours after the second injection. In 1 of these the spinal fluid remained sterile after the third injection and in the other after the fifth injection. Further, in 2 patients receiving penicillin every twelve hours the spinal fluid cultures were sterile after the first injection of penicillin, yet the direct smears showed organisms until two and five injections, respectively, were given. These findings suggest that sufficient penicillin is present in the spinal fluid after twelve hours, and occasionally after twenty-four hours, to inhibit the growth of bacteria on the culture medium. It is important, therefore, to correlate the bacteriologic findings with the clinical course and to observe the criteria set forth in our plan of treatment.

The total amount of penicillin administered intravenously and/or intramuscularly varied considerably (20,000 to 900,000 units), the first patients treated receiving the largest amounts. We soon observed that the total dosage could be reduced considerably without risk to the patient. Thus, 55 patients received between 20,000 and 250,000 units of penicillin intravenously and intramuscularly, and 35 of these received 100,000 units or less. One patient, seen several hours after the onset of his illness, recovered without any penicillin intravenously or intramuscularly. Among the patients without bacteremia, no appreciable difference in the outcome and course of the disease was perceptible in the group treated with 20,000 to 50,000 units when compared with those receiving as much as 900,000 units. Nor was there any correlation between the amount of penicillin given by these routes and the amount of intrathecal penicillin required for recovery. Of 10 patients in whom positive blood cultures were found, in 4 the blood was sterile after 40,000 to 50,000 units, in 5 after 70,000 to 125,000 units and in 1 after 250,000 units. In 2 of these the blood was sterile after 105,000 to 110,000 units, but in each penicillin was continued until 200,000 units had been given. As 250,000 units was administered to the patient with the "Waterhouse-Friderichsen syndrome" this dose may represent the maximum amount required to combat the severe forms of meningococcemia unless circulatory failure is too far advanced when the patient is admitted to the hospital.

Acute monarthritis or polyarthritis was present in 15 patients on admission and was uninfluenced by the intravenous and intramuscular administration of as much as 900,000 units of penicillin. In 9 individuals

aspiration of the affected knee joints revealed cloudy yellow fluid containing 20,000 to 100,000 polymorphonuclear leukocytes per cubic millimeter. In 8 the aspirated fluid was sterile, while, in the other, meningococci were found on direct smear and on culture. Intra-articular penicillin (10,000 units) was administered to 2 of the patients with sterile synovial fluid, but no beneficial effects were observed. In the patient from whose joint meningococci were recovered, the fluid became sterile after the intra-articular injection of 10,000 units of penicillin on two successive days.

Acute epididymitis, alone or with orchitis, developed in 10 patients. It usually appeared on the sixth to the seventh day of illness, although it was noted as early as the second day and as late as the tenth day. Its occurrence was unrelated to the amount of penicillin administered intravenously and intramuscularly. Three patients were treated with 150,000 to 160,000 units of penicillin over a period of forty-eight hours after the onset of acute epididymo-orchitis, but in none was the period of resolution shortened. In these as in the other 6 patients, spontaneous recovery ensued.

In 3 patients transient diplopia was observed without manifest cranial nerve involvement. Left sixth nerve palsy developed on the second day of admission in 3 of the most severe cases encountered in this series; in 1 of these it was followed twenty-four hours later by paresis of the right sixth nerve. In 2, restoration of function was ultimately complete; in the other, slight diplopia on extreme abduction remained. In 1 patient with fulminating meningococcemia slight transient third nerve paresis was noted. Acute fibrinous pericarditis was found on admission in 1 patient and was unaffected by 715,000 units of penicillin given intravenously and intramuscularly. In 4 patients acute tonsillitis and in another unilateral acute otitis media complicated the convalescence. In 2 instances acute thrombophlebitis of the saphenous vein developed on the fifth and sixteenth days, respectively, and was unrelated to the site of therapy.

Hemolytic Streptococcus Meningitis.—All 3 patients with meningitis due to hemolytic streptococci recovered completely following two intrathecal injections of penicillin. The spinal fluid was sterile twenty-four hours after the first injection, and the temperature returned to normal in four to six days. The patient with bacteremia was given 400,000 units intravenously and intramuscularly over a period of fifty-three hours. Blood drawn for culture on the fifth day was sterile. One of the patients without bacteremia received only 170,000 units of penicillin intravenously and intramuscularly over a period of thirty-nine hours. The temperature returned to normal within six days. The other patient with meningitis secondary to bilateral acute otitis media was given 650,000 units of penicillin intramuscularly over a period of eight and one-half days, although the temperature was normal in five days. No surgical intervention was necessary in this instance.

Streptococcus Viridans Meningitis.—Both patients recovered from meningitis, one following three and the other after four intrathecal injections of penicillin. The blood cultures were sterile in 1 patient after 40,000 units intravenously and in the other after 130,000 units intravenously and intramuscularly. However, penicillin was continued until 200,000 and 300,000 units, respectively, had been administered over periods of three to four days. The temperature returned to normal after three to five days. No sequelae were demonstrable, though both patients were comatose for twenty-four hours after therapy was begun.

Pneumococcic Meningitis Secondary to Acute Otitis Media.—Although there was only 1 patient with pneumococcic meningitis in our series, it is of interest that complete recovery followed three intrathecal injections of penicillin and 800,000 units given intravenously and intramuscularly over a period of ten and one-half days. The spinal fluid cultures remained positive until the third intraspinal injection of penicillin was administered. In view of the presence of acute otitis media and the possibility of bony suppuration in the areas adjacent to the middle ear, intramuscular penicillin was continued until the temperature remained normal for five days. Convalescence progressed uneventfully thereafter without surgical intervention.

UNTOWARD EFFECTS

In those patients who received penicillin intrathecally every twelve hours, as well as in some individuals who were given intrathecal doses of 15,000 units, more severe and more persistent headache was noted, fever was prolonged and signs of meningitis subsided more slowly. The irritating effect of penicillin on the meninges, when injected intrathecally, was previously demonstrated by Rammelkamp and Keefer [4] and by Pilcher and Meacham.[5] Further, we observed that penicillin produced by different manufacturers caused various degrees of meningeal irritation. Thus, the dark brown product was found to have the greatest irritant effect and caused febrile reactions, whereas the pale yellow product had the least demonstrable irritant effect. It is our belief, therefore, that the dark brown powder should not be used intrathecally. Localized thrombophlebitis developed in 4 patients at the site of the continuous intravenous injections but was of minor significance. In 3 patients with cerebrospinal fever mild transitory urticaria was noted within twenty-four hours after therapy was started. Whether this should be ascribed to the penicillin or to the disease per se cannot be stated. No other local or toxic effects were observed.

COMMENT

The effectiveness of penicillin in the treatment of meningococcic infections in man is clearly demonstrated by the recovery of 64 out of 65 patients with cerebrospinal fever. That penicillin is also a potent agent in the control of meningitis caused by Streptococcus haemolyticus, Streptococcus viridans and pneumococcus is indicated by the recoveries observed in our small series of 6 patients. Contrary to the reported experiences with other infections, relatively small amounts of intravenous and/or intramuscular penicillin (40,000 to 250,000 units) were required to sterilize the blood stream in our cases of meningococcemia. Further, it was not necessary to continue penicillin for long periods of time, eight to forty-eight hours of therapy being adequate for these patients. It seems logical to assume that, when combined with intrathecal therapy, these data are equally applicable to the treatment of the nonbacteremic cases, the larger doses being employed in the more serious types of infection. On the other hand, in meningitis secondary to otitis media, intravenous or intramuscular penicillin must be continued until all other sources of infection have been adequately controlled. The majority of patients with cerebrospinal

5. Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infections: III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin, J. A. M. A. **123**: 330 (Oct. 9) 1943.

fever received only one or two injections of penicillin intrathecally, whereas in the most severe infections as much as five injections were necessary for recovery. It would appear safer, however, to administer a minimum of two intrathecal injections of 10,000 units each to all patients, even though many of the milder or earlier infections may be controlled by a single injection. As 2 patients without bacteremia recovered following only 20,000 units intravenously and 10,000 units intrathecally, and another recovered with intrathecal therapy alone, the question may be raised whether any intravenous or intramuscular penicillin is indicated in the nonbacteremic cases. Since the clinical picture presented by patients with bacteremia is often indistinguishable from that observed in individuals with negative blood cultures, it is our belief that penicillin should be administered intravenously or intramuscularly to all patients with meningitis. Moreover, it is of the utmost importance to continue penicillin intrathecally until recovery is assured, observing the criteria outlined in our plan of treatment. The findings of Pilcher and Meacham [5] in experimental meningitis support the latter contention.

The failure of penicillin to alter the course of arthritis or pericarditis was not unexpected. Similar failures have been observed with sulfonamide therapy.[6] It is probable that neither of these agents is excreted into these spaces in sufficient amounts, if any, to be effective. The occurrence of epididymitis, with or without orchitis, in 10 patients with cerebrospinal fever is of interest, as it is generally regarded as rare. However, it has been found quite frequently in some epidemics [7] and has also been observed following sulfonamide therapy.

We are fully cognizant of the shortcomings of any therapeutic agent requiring intrathecal administration to achieve its maximum effectiveness. Notwithstanding, it is evident from our experiences that for those patients who develop reactions to the sulfonamides, or in whom sulfonamide therapy is contraindicated for other reasons, for those who are sulfonamide resistant and for those with the fulminating bacteremias wherein a highly potent agent is indicated, penicillin alone may prove life saving. It is not unlikely that, when ultimately prepared in a more concentrated and more highly purified form, free from pyrogens, penicillin may be excreted into the subarachnoid spaces in sufficient amounts following intravenous or intramuscular administration to justify the abandonment of intrathecal therapy. Until then, penicillin should be administered intrathecally as well as intravenously or intramuscularly in the treatment of meningitis.

SUMMARY AND CONCLUSIONS

1. Penicillin was administered intrathecally and intravenously or intramuscularly to 65 patients with cerebrospinal fever (11 with bacteremia), 3 patients with hemolytic streptococcus meningitis (1 with bacteremia and 1 with acute otitis media), 2 patients with streptococcus viridans bacteremia and meningitis and 1 patient with pneumococcic meningitis secondary to acute otitis media. Seventy of the 71 patients recovered. Except for slight unilateral paresis of the sixth cranial nerve in 1 patient, no sequelae were observed.

2. Although one intrathecal injection of 10,000 units controlled some of the milder or earlier infections, a minimum of two injections is advocated as a precautionary measure. In the severe infections as much as five intrathecal injections (50,000 units) were required. Bacteremia was controlled by 40,000 to 130,000 units of penicillin intravenously and intramuscularly in the majority of instances. In a patient with fulminating meningococcemia and "Waterhouse-Friderichsen syndrome," 250,000 units over a period of forty-eight hours was followed by recovery. In meningitis secondary to otitis media more prolonged intravenous or intramuscular therapy is indicated.

3. Intravenous and intramuscular penicillin is ineffective in the treatment of such complications of meningococcemia as acute arthritis, epididymitis, orchitis or pericarditis.

4. Penicillin administered both intrathecally and intravenously or intramuscularly is an effective, highly potent agent in the treatment of meningitis. No significant untoward effects are demonstrable.

ADDENDUM.—Since the preparation of this paper penicillin was administered to 11 other patients with cerebrospinal fever. All of them recovered. For 2 patients who had manifested symptoms of meningitis for one week prior to hospitalization, six intrathecal injections of penicillin (60,000 units) were required.

6. Jaeger, H. W.: Meningococcic Infection of Joints, Rev. chilena de pediat. **14**: 414 (June) 1943. Rundlett, E.; Gnassi, A. M., and Price, P.: Meningococcic Meningitis: Prognostic Significance of the Spinal Fluid Sugar, J. A. M. A. **119**: 695 (June 27) 1942.

7. Brinton, D.: Cerebrospinal Fever, Baltimore, Williams & Wilkins Company, 1941, p. 51.

ABSTRACT OF DISCUSSION

DR. WALLACE E. HERRELL, Rochester, Minn.: In view of the sensitivity of Neisseria intracellularis to penicillin, it is not surprising that such satisfactory results have been obtained. In 90 per cent of certain cases recovery will follow the use of sulfadiazine or one of the other sulfonamides. Penicillin, however, is an agent which appears relatively free of any serious toxic reactions. When greater supplies of penicillin are available it seems likely that it may be possible, as well as desirable, to treat all of these patients with penicillin without waiting for failures to occur with sulfonamides. This might well result in even greater success than has been attained in the past. It is my opinion that meningitis due to the several organisms isolated in 6 of the 71 cases reported by the authors will be found to respond in a less satisfactory manner to penicillin. It is the experience at the present time that probably no better recovery rates than 60 per cent have been experienced with penicillin. The plan of treatment which has been outlined is an exceedingly satisfactory one. In addition to being administered by the intrathecal route, penicillin also should be given intramuscularly or intravenously in cases of meningitis. It is interesting that Rosenberg and Arling have found that relatively small amounts of penicillin (250,000 units) have been satisfactory. In meningitis due to pneumococci or streptococci I believe that larger amounts of penicillin will be required for the total dose and that the course of treatment will necessarily be somewhat longer. In connection with the arthritis complicating meningococcic meningitis, it is at times difficult to isolate the organism from the joint fluid. Nevertheless I am inclined to believe that there was definitely some beneficial effect. A positive culture was obtained in only 1 of 9 cases of septic arthritis in which cultures were made. Using Fleming's modification of the Wright slide cell technic, my associates and I have made determinations of the concentration of penicillin in the joint fluid of patients receiving this agent. In many instances we have found satisfactory antibacterial amounts of penicillin in the joints. The ratio of blood to joint fluid content is approximately 2 to 1. Urticaria or irritative dermatitis has been observed by us in 2 of 150 cases. I believe this skin reaction will be observed more frequently as more and more penicillin is used. Many people are sensitive to molds and to mold products. One must exercise caution in the presence of irritative dermatitis or severe urticaria. Continuing to force penicillin might result in the development of an exfoliative dermatitis, although at times one may administer penicillin without difficulty to patients who have previously exhibited this reaction.

LIEUTENANT COMMANDER DAVID H. ROSENBERG (MC), U.S.N.R.: Dr. Herrell's comments regarding arthritis are of interest. Our observations were based on the duration of the symptoms and signs of arthritis. It is apparent that the effects of penicillin in these complications should also be studied by assays of the penicillin content of the affected joints.

PENICILLIN AND SKIN GRAFTING

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DETROIT

Few patients are more miserable than those with large unhealed third degree burns. Early skin grafting of the burned areas is the only means of quickly returning these patients to a useful life. The longer this procedure is delayed, the greater the immediate threat of death and the ultimate development of scars and deformity. The aim of all treatment, therefore, is reepithelization of the burned areas as promptly as possible. In general, it requires from one to three months to achieve this aim. The chief causes for the prolonged healing are (1) the necessity of deferring grafting until the burned tissue has sloughed and the granulating bed is ready to accept a graft, (2) the necessity for multiple grafting operations because of the lack of sufficient donor sites or the inability of the patient to tolerate grafting of the entire burn at one time and (3) the necessity of grafting the same area more than once because previous grafts have partially or completely failed to take.

Harvey and Connor [1] have devised a method of rapidly removing the dead tissue. Ordinarily it requires fifteen to forty days for burned tissue to separate. By shortening this time to a few days they have overcome one of the greatest factors prolonging the convalescence of burned patients. Although lack of donor sites will always remain as a limiting factor, improvements in the care of burned patients have made it possible and will continue to make it possible to graft larger areas at one operation. The necessity of grafting the same area more than once remains, therefore, as the chief factor tending to prolong the convalescence of these patients.

Skin grafts fail to take because of (1) infection, (2) failure to maintain the graft in contact with the recipient site and (3) the lack of adequate blood supply in the recipient site. Any one skilled in the art of skin grafting has at his command the means of maintaining a skin graft in contact with the recipient site and of insuring an adequate blood supply for the graft. However, in spite of the most careful preparation of the granulating bed a certain number of split thickness grafts are partially or completely lost because of infection.

Padgett [2] reported the percentage of takes of a large series of split thickness grafts applied to contaminated and to aseptic recipient sites. The analysis of his results (table 1) shows that infection is the most common cause of partial or complete loss of such a graft.

In approximately one third of the cases in which grafts were placed on contaminated recipient sites, 25 per cent or more of the graft was lost. In only about two thirds of these patients were satisfactory takes obtained in which only 10 per cent or less of the graft was lost. In contrast, satisfactory takes were obtained in 98 per cent of the grafts done on aseptic recipient sites. Furthermore, a review shows that many patients whose first grafts failed also lost large parts of successive grafts. This has been our experience and has usually been due to infection of the granulating bed with sulfonamide resistant Streptococcus haemolyticus or Staphylococcus aureus.

A large denuded area of the body usually becomes infected with Pseudomonas pyocyaneus, Proteus vulgaris, Escherichia coli or other gram negative bacilli of intestinal origin. There is yet no chemotherapeutic agent that will adequately control these organisms. Fortunately, in most cases they seem to act primarily as saprophytes and do not interfere with the growth of split thickness grafts. Many burns, however, become infected with beta hemolytic streptococci, Staphylococcus aureus and other coagulase positive micrococci. It is these organisms that are responsible for the failure of skin to grow when transplanted to granulating surfaces. Although the sulfonamides control many hemolytic streptococcus infections, they are ineffective against the occasional resistant strain and against Staphylococcus aureus and the other coagulase positive micrococci. While their use has improved the results of skin grafting, especially in the presence of susceptible hemolytic streptococci, it has not solved the problem.

TABLE 1.—*Padgett's Results*

Percentage of Graft Lost	Number of Cases	
"Fresh Burns"		
Total grafts	44	
0 - 10	28 (63.6%)	In 31.8% of the cases 21% or more of the graft was lost
11 - 20	2 (4.5%)	
21 - 25	1 (2.3%)	
26 - 40	1 (2.3%)	
41 - 100	12 (27.2%)	
Grafts on Other Obviously Contaminated Recipient Sites		
Total grafts	17	
0 - 10	9 (52.9%)	In 35.3% of the cases 21% or more of the graft was lost
11 - 20	2 (11.8%)	
21 - 30	2 (11.8%)	
31 - 100	4 (23.5%)	
Grafts on Aseptic Recipient Sites		
Total grafts	151	
0 - 10	148 (98%)	In only 2% of the cases 11% or more of the graft was lost
11 - 25	2 (1.4%)	
26 - 100	1 (0.6%)	

Penicillin is an extremely powerful bacteriostatic and bactericidal agent that has the advantage of acting not only against Streptococcus haemolyticus but also against Staphylococcus aureus. It seemed important, therefore, to determine whether its administration at the time of skin grafting would improve the percentage of takes.

Nineteen split thickness grafts were performed on 17 patients who were receiving penicillin intramuscularly. In general, grafting was done as soon as the slough had separated, usually three to four weeks after the burn had occurred. In 5 instances, however, grafting was delayed because of (1) the slow separation of a deep slough, (2) the necessity for multiple operations or (3) the admission of patients to our hospital some time after they had been burned. The initial dressings consisted of a wide variety of substances, zinc oxide ointment, glass cloth and cellucotton, zinc

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1. Harvey, S. C., and Connor, G. J.: The Healing of Deep Thermal Burns, read before the American Surgical Association, Chicago, May 3, 1944.

2. Padgett, E. C.: Skin Grafting, Springfield, Ill., Charles C Thomas, Publisher, 1942.

TABLE 2.—*Details of Treatment*

Patient	Age	Days Elapsing Between Injury and Grafting	Location	Size of Graft	Cultures Before Grafting	Cultures at First Dressing	Dosage of Penicillin	Percentage of Take
A. T.	83	28	Shoulder and arm	65 sq. in.	M. aurantiacus coagulase —; diphtheroids	M. aurantiacus coagulase —; diphtheroids; gram + cocci	10,000 units every 2 hours for 5 doses before grafting 10,000 units every 2 hours for 5 days after grafting	100%
J. B.	52	.. .	Foot	30 sq. in.	Ps. pyocyaneus; diphtheroids	M. aurantiacus coagulase —; M. epidermidis coagulase —; B. coli; diphtheroids	None before grafting 5,000 units every hour for 5 days after grafting	100%
M. M.	30	30	Thighs	35 sq. in.	M. aurantiacus coagulase —; Ps. pyocyaneus; diphtheroids	M. epidermidis coagulase —; M. aurantiacus coagulase +; Ps. pyocyaneus; diphtheroids; aerobic gram + rods	5,000 units every hour for 12 doses before grafting 5,000 units every hour for 5 days after grafting	95%
W. C.	52	66	Leg and foot	90 sq. in.	M. varians coagulase +; Ps. pyocyaneus; Ps. fluorescens; aerobic gram + rods	Gram + rods; Ps. fluorescens; Ps. pyocyaneus	5,000 units every hour for 18 hours before grafting 5,000 units every hour for 5 days after grafting	100%
B. P.	40	25	Shoulders and scalp	54 sq. in.	M. varians coagulase +; Ps. fluorescens; M. tetragenes; aerobic gram + rod	M. varians coagulase +; Ps. fluorescens; diphtheroids	10,000 units every hour for 18 hours before grafting 10,000 units every hour for 4 days after grafting	95%
I. S.	5	20	Back and chest	50 sq. in.	M. aurantiacus coagulase +; beta hemolytic streptococcus; B. coli; diphtheroids; B. alkaligenes	Ps. pyocyaneus; diphtheroids; M. epidermidis coagulase +	5,000 units every hour for 24 hours before grafting 5,000 units every hour for 4 days after grafting	95%
C. H.	10	180	Chest, axilla and arm	125 sq. in.	M. varians coagulase +; gram + rod; gram neg. rod; M. aurantiacus coagulase +; M. epidermidis coagulase —	M. varians coagulase +; diphtheroids	5,000 units every hour for 5 days before grafting 5,000 units every hour for 9 days after grafting	95% (This loss was due to hematoma beneath graft)
D. T.	3	20	Chest and abdomen	30 sq. in.	M. aurantiacus coagulase +; M. varians coagulase +; diphtheroids; gram neg. rods	M. aurantiacus coagulase +; diphtheroids; B. coli; B. aerogenes	None before grafting 5,000 units every hour for 2 days after grafting, then 2,500 units every hour for 3 days after grafting	100%
B. M.	5	60	Knee	50 sq. in.	Ps. pyocyaneus; M. epidermidis coagulase —	Ps. pyocyaneus; diphtheroids; M. epidermidis coagulase +	5,000 units every hour for 18 hours before grafting 5,000 units every hour for 2 days after grafting, then 2,500 units every hour for 3 days after grafting	95%
R. B.	5	40	Arms and shoulders	42 sq. in.	M. aurantiacus coagulase +; Ps. pyocyaneus	M. aurantiacus coagulase +; Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 4 days after grafting	90%
B. M.	38	30	Leg	16 sq. in.	M. aurantiacus coagulase +; M. epidermidis coagulase —; Ps. pyocyaneus; aerobic gram + rod	Beta hemolytic streptococcus; Ps. pyocyaneus; M. epidermidis coagulase —	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 4 days after grafting	95%
C. W.	1	19	Chest	30 sq. in.	M. varians coagulase +; B. coli; beta hemolytic streptococcus; aerobic gram + rod	Ps. pyocyaneus; gram + rod	1,000 units every hour for 12 hours before grafting 1,000 units every hour for 5 days after grafting	95%
L. W.	10	25	Trunk	135 sq. in.	Ps. pyocyaneus	Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	90%
L. W.	10	44	Trunk	30 sq. in.	Ps. pyocyaneus; Proteus vulgaris	Ps. pyocyaneus; Proteus vulgaris	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	100%
R. M.	43	25	Thigh	60 sq. in.	M. varians coagulase +; Proteus vulgaris; Ps. pyocyaneus	Proteus vulgaris; Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 5.000 units every hour for 5 days after grafting	80%
J. V.	52	28	Hand	28 sq. in.	Ps. pyocyaneus; M. aurantiacus coagulase +; M. varians coagulase +; B. aerogenes	M. aurantiacus coagulase —; Ps. pyocyaneus; B. aerogenes; aerobic gram + rod	5.000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	100%
G. R.	10	25	Thighs	160 sq. in.	Proteus vulgaris; beta hemolytic streptococcus; Staph. aureus	Proteus vulgaris; Beta hemolytic streptococcus; Staph. aureus	5,000 units every hour for 12 hours before grafting 5,000 units every hour for 5 days after grafting	90%
G. R.	15	43	Leg	72 sq. in	Proteus vulgaris; Ps. pyocyaneus	Proteus vulgaris; Ps. pyocyaneus	5,000 units every hour for 12 hours before grafting 10,000 units every 2 hours for 5 days after grafting	85-90%
J. C.	46	25	Arm and hand	64 sq. in.	M. varians coagulase +; M. aurantiacus coagulase +; B. coli	None	5,000 units every hour for 24 hours before grafting 5,000 units every hour for 24 hours after grafting	100%

peroxide in a carbowax base, and several other experimental ointments. The dressings were changed at intervals of five to fourteen days, depending on the patient's condition and the requirements of certain studies that were in progress on these patients. In only 2 instances were wet dressings employed. At the time of grafting the dressings were removed in the operating room, and the exudate was washed away with warm isotonic solution of sodium chloride. If the granulations were excessive they were cut away; otherwise the grafts, which were cut with the Padgett dermatome, were placed directly on the granulating bed and held in place with fine silk sutures. A single layer of fine mesh gauze impregnated with zinc oxide ointment was placed next to the graft. This was covered with a few layers of ordinary gauze, and the entire area was then covered with mechanics' waste and wrapped with elastic bandage. The initial dressing was changed on the fourth, fifth or sixth day.

All the patients received penicillin intramuscularly. The dose and the duration of therapy varied somewhat from patient to patient. In general, therapy was started about twelve hours before operation and was continued until the time of the first dressing. The exact details of therapy are given in table 2. With one exception, from 90 to 100 per cent of the transplanted skin took in every instance. The exception occurred in an uncooperative alcoholic addict who had third degree burns of the perineum, both thighs and legs. Only 80 per cent of the grafts placed on his groin and thighs took. The loss in this case was probably due to failure of the dressings to hold the grafts in place.

The loss in all cases occurred at the margin of the grafts where they overlapped the new epithelium growing in from the margins of the burned area. This thin layer of new epithelium prevents the graft from taking, and, unlike normal skin, it is not strong enough to survive when covered with a graft. The result is a slough of both the new epithelium and the margin of the graft. If the new epithelium is cut away and the graft joined to normal skin, this marginal loss does not occur.

The administration of penicillin did not seem to alter the bacterial flora a great deal; cultures taken at the time of the first dressing from the margins of the grafts and from the sutures usually yielded the same organisms that were present on the granulating surface before grafting. In spite of their persistence, they did not seem to affect the growth of the graft. Penicillin, therefore, must hold them in check until the skin has a chance to become established in its new bed.

Though penicillin has been administered to only 17 patients at the time of skin grafting, we believe that its use has the following definite advantages:

1. It permits early grafting. Split thickness grafts can be successfully applied as soon as the slough has separated without further time consuming preparation of the granulating area.

2. It appears to prevent the loss of skin from infection that ordinarily occurs in about one third of the cases in which split thickness grafts are placed on contaminated recipient sites.

Before penicillin was available, we performed over a hundred grafts in patients with third degree burns. Although many excellent takes were obtained, in about one third of the cases 25 per cent or more of the graft was lost because of the occurrence of infection. Therefore the consistency with which excellent takes were obtained in this series of 19 grafts has been very impressive to us. We are presenting the method with the hope that others will try it.

TREATMENT OF OSTEOMYELITIS OF THE FACIAL BONES WITH PENICILLIN

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One of the most serious complications of sinusitis is osteomyelitis of the facial bones. This may occur either following surgical operation or by direct extension from the diseased sinuses. In either instance the outlook has always been very poor, for, in spite of sulfonamides and operative intervention, the infection tends to extend throughout the bone and to spread to the brain and meninges, with a mortality in severe cases of as high as 80 per cent. With penicillin, however, there was every reason to think that the prognosis might be greatly altered, for this powerful bacteriostatic agent might hold the infection in check until adequate surgery could be performed. The cases reported here, in which brilliant results were obtained, showed that such was the fact and are reported because they illustrate the technical problems both of penicillin administration and of surgical treatment.

CASE 1.—*Development of cellulitis and osteomyelitis following intranasal maxillary antrotomy; no response to sulfonamides; prompt response to penicillin, with three relapses; complete cure after removal of all necrotic bone.*

Mrs. M. W., a woman aged 32, housewife, who entered Stanford Hospital on Sept. 24, 1943, had had chronic sinusitis for four years, and four weeks before entry a right intranasal maxillary antrotomy was performed. A week later pain and swelling developed in the soft tissues overlying the antrum. A wisdom tooth was removed, allowing pus to drain into the mouth through the empty socket, but the pain and swelling of the face did not subside. Sulfathiazole 6 Gm. a day for two weeks was administered in another hospital with no improvement. On entry the temperature was 38.5 C. (101.3 F.), pulse rate 86, respiratory rate 16 and blood pressure 115/70. The patient, a slender woman in good general physical condition, was very uncomfortable because of the pain and swelling of the face. The right eye was nearly shut, and the swelling extended down to the mouth, obliterating the nasolabial fold. The overlying skin was red and glistening, and there was definite fluctuation just below the eye. In the mouth, thick yellow pus was draining from the empty tooth socket and from a small fistula in the center of the hard palate. The right nostril was filled with thick yellow purulent exudate. Apart from these local findings, physical examination revealed no abnormalities.

The red blood cell count was 4,100,000; hemoglobin, 70 per cent; white blood cell count, 12,200, with a normal differential count; the erythrocyte sedimentation rate (Wintrobe) was 44 mm. per hour; packed cell volume was 38, and the urine was normal.

Details of the course in the hospital are shown graphically in the accompanying chart. The day following entry a continuous intravenous infusion of penicillin was begun, and two hours later an operation was performed. Widespread destruction of the right maxilla required extensive removal of the lateral and inferior aspects of the maxilla, including the hard palate nearly to the midline. The antrum was filled with pus, and the pterygoid plate, roof and posterior wall of the antrum were removed. The soft tissue abscess of the face was found to drain freely into the space left by removal of

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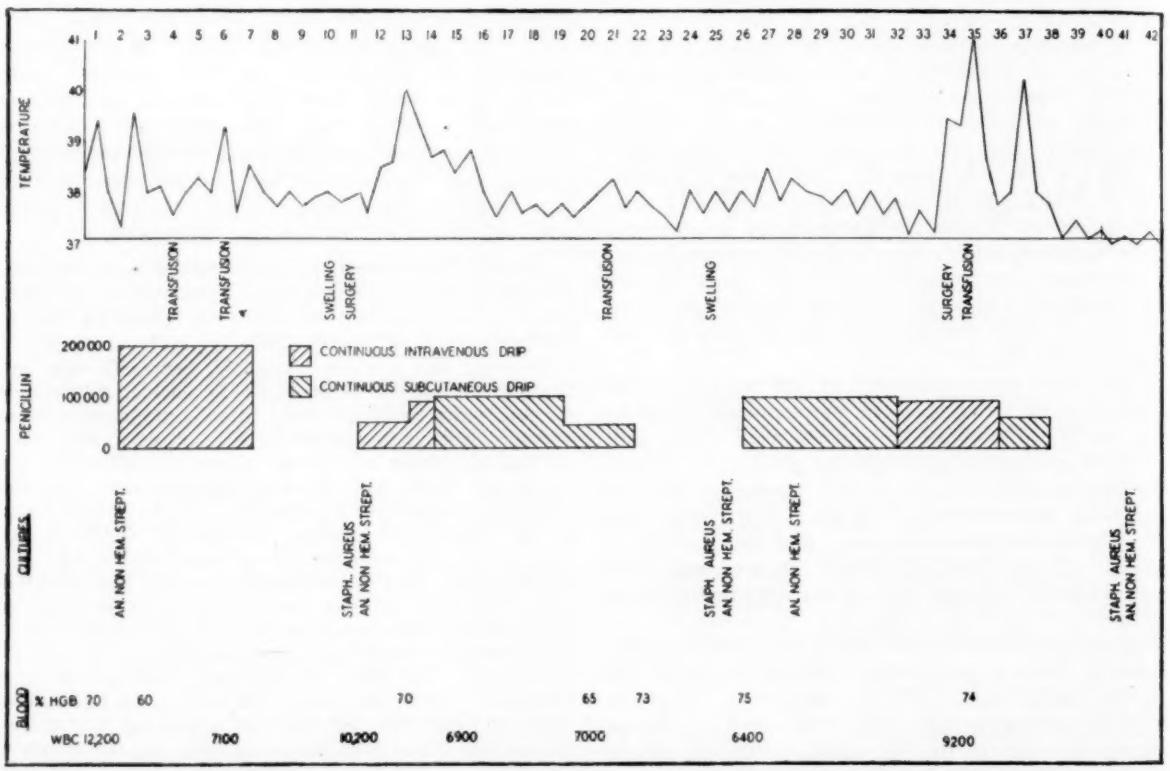
The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigation recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

bone, and for this reason no external incision was made. Devitalized bone was removed as completely as possible, the sharp edges were smoothed, and the entire cavity was packed with iodoform gauze.

Cultures of bone removed at operation revealed a heavy growth of anaerobic nonhemolytic streptococci. Sections of the bone showed areas of necrosis and inflammation indicative of subacute osteomyelitis.

Administration of penicillin 200,000 units a day by continuous intravenous infusion in 1 liter of isotonic solution of sodium chloride was continued during operation and afterward for five days, a total of 1 million units. Two transfusions and fairly heavy sedation were the only other therapeutic measures. There was, during this five day period, a dramatic diminution of the swelling and tenderness of the face, but a recurrence was predicted because denuded, apparently necrotic, maxillary bone could be palpated with forceps along the infraorbital ridge, high in the cavity left by the operation.

After five days penicillin therapy was instituted for the third time because of a recurrence of swelling, tenderness and pus at the local site. A pure culture of anaerobic nonhemolytic streptococci was obtained from the pus. After seven days' treatment by the subcutaneous route approximately 100,000 units daily, the patient was again operated on. In addition to extraction of all remaining portions of apparently devitalized maxillary bone along the infraorbital ridge, the right upper central incisor and the remainder of the right side of the hard palate were removed. There was again a severe postoperative febrile reaction, probably due to impurities in the penicillin solutions. The penicillin was discontinued two days after the operation, a total of 900,000 units during this ten day course, and a final total of 2,690,000 units since entry. The temperature quickly returned to normal, and this time the swelling and tenderness did not recur. The facial incision healed rapidly, and the patient left the hospital ten days after the last operation. Cultures of the cavity in the mouth still revealed a heavy growth



Course in case 1.

Three days after the penicillin was stopped there was a sudden reappearance of pain and swelling below the right orbit, and an external incision 4 cm. in length was made parallel to, and 0.5 cm. beneath, the lower margin of the orbit. The soft tissues were edematous, but little frank pus was encountered. Cultures revealed large numbers of both anaerobic nonhemolytic streptococci and Staphylococcus aureus (coagulase positive). The underlying maxillary bone was denuded of periosteum, but no bone was removed because definite sequestration had not yet occurred. The wound was packed open with iodoform gauze and pencillin therapy was begun by the continuous intravenous route, 50,000 units a day. A severe febrile reaction, probably caused by pyrogenic saline solution in which the penicillin was mixed, necessitated a change to the continuous subcutaneous route after 175,000 units had been administered. A total of 810,000 units was given intravenously and subcutaneously during this course of eleven days. Again the swelling and tenderness disappeared completely, and very little pus was present in the wound. Cultures were repeatedly positive for S. aureus (coagulase positive) and anaerobic nonhemolytic streptococci.

of anaerobic nonhemolytic streptococci and S. aureus (coagulase positive).

During a six months follow-up period the patient has remained entirely well and is now having a prosthesis made to replace the bony structures which were removed surgically.

CASE 2.—*Failure of sulfonamides and extensive surgical procedures to cure osteomyelitis of maxillary bone following sinusitis; prompt response to penicillin, with several relapses; complete cure with penicillin plus removal of all foci of dead bone.*

B. P., a man aged 23, a dyecaster, who entered the San Francisco City and County Hospital in December 1942, suffered from acute right frontal sinusitis and osteomyelitis of the frontal bone. Surgical exploration revealed a widespread purulent destruction of the frontal bone and a large extradural abscess. Approximately one-half the frontal bone was removed to well beyond the limits of infected bone, and both frontal sinuses were obliterated. The T shaped incision was packed open for the following two months, during which time convalescence was uneventful. A secondary closure of the wound was then accomplished with excellent healing except for a small

persistent fistula in the midline at the juncture of the flaps. Three months after entry the patient was discharged and thereafter followed regularly in the Stanford University outpatient clinic. All attempts to close this fistula met with failure. Repeated x-ray studies revealed a persistent left anterior ethmoiditis and after much investigation it was felt that the fistula was being fed by this ethmoid infection. In July 1943 the patient entered Stanford Hospital, where external ethmoidectomy and excision of the fistulous tract was performed. S. aureus was cultured from the operative area. Convalescence was uneventful, and the patient was discharged on the sixth postoperative day. Twelve days after the operation he complained of frontal headache and pain in the left malar region. Examination revealed tender swelling along the left infraorbital ridge and swelling of the operative wound with slight fluctuation. The patient reentered the hospital, where the wound was opened widely, releasing a small amount of purulent discharge. Palpation of the depths of the wound with forceps revealed the frontal process of the left maxilla to be denuded of periosteum, and S. aureus was again isolated from the pus. These findings seemed to indicate an osteomyelitic process proceeding along the superior ramification of the left maxilla. Full doses of sulfadiazine (6 Gm. a day) were given over the following eighteen days, and supportive treatment consisted of blood transfusions, vitamin therapy and a high calory diet. Excellent drainage was secured from the infected area. In spite of this treatment the patient's temperature was septic; he appeared very toxic and continued a steady downhill course. The left intraorbital swelling progressed slowly until the left eye was entirely closed and the malar swelling extended into the left temporal region. X-ray examination revealed an early destructive process extending along the left infraorbital ridge laterally to the infraorbital foramen.

S. aureus and anaerobic nonhemolytic streptococci were cultured on two occasions from pus expressed from beneath the swollen area through a small opening just below the medial side of the left orbit. Since sulfonamide therapy seemed ineffectual in controlling the spread of the disease, penicillin was begun on August 30 by continuous intravenous drip, 60 units per cubic centimeter, a total of 50,000 units in seventeen hours. Because of venous thrombosis, a change was then made to the continuous subcutaneous route, 100,000 or 200,000 units daily, a total of 1,385,000 units in twelve days. There was decided subjective improvement within twelve hours after the penicillin was started, and during the next ten days the pain and swelling disappeared completely. Daily cultures revealed S. aureus and anaerobic nonhemolytic streptococci for five days, S. aureus alone for the next three, and thereafter the drainage ceased altogether.

Five days after penicillin was stopped the pain and swelling recurred, accompanied by a temperature rise to 38.2 C. (100.7 F.) and white blood cell count of 9,600. Penicillin was started intravenously 200,000 units daily for five days, and the incision below the medial side of the left eye was extended laterally 1 centimeter beyond the infraorbital foramen. Pus obtained at the operation contained only anaerobic nonhemolytic streptococci. Again the swelling and pain promptly subsided, but penicillin therapy was reinstituted after a four day interval, 100,000 units daily for three days, in conjunction with the surgical removal of a sequestrum through the facial incision. The patient then went home but returned again ten days later with swelling and inflammation below the left eye. After five days of continuous penicillin therapy, partly intravenous and partly subcutaneous (total, 320,000 units) he was clinically well and left the hospital because of the death of his mother. Two small sequestrums were removed from the outer edge of the wound during this hospitalization. Ten days later there was another typical recurrence, and this time packs soaked with penicillin 100 units per cubic centimeter were placed in the wound every three hours for four days. Surgical exploration revealed two more small sequestrums in the outer edge of the wound, but the underlying exposed bone appeared healthy when they were removed. The wound closed quickly when the packs were discontinued, and the patient went home on October 27, having received a total of 3,010,000 units of penicillin. He has been entirely well during a follow-up period of over five months.

CASE 3.—*Cellulitis of jaw following tooth extraction; involvement of orbit with protrusion and blindness, and osteomyelitis of frontal bone; cure with penicillin after failure with surgical procedures and sulfonamides.*

G. S., a white man aged 38, a farmer, developed a painful swollen right jaw in September 1943 three days after the extraction of two upper molar teeth. The cellulitis spread rapidly, causing protrusion and complete blindness of the right eye. On September 30 he was admitted to another hospital, where his temperature was 106 F., and x-ray examination showed clouding of the right antrum but no signs of osteomyelitis. After two weeks of therapy with full doses of sulfadiazine he went home much improved but returned four days later with a recurrence of fever, headache and periorbital swelling. X-ray examinations now showed involvement of the right sphenoid and ethmoid cells as well as of the right antrum. During the next two months he was given repeated courses of sulfonamides, and several subcutaneous abscesses below the right eye were drained surgically. On December 5 an incision was made through the right brow, releasing 5 cc. of creamy pus, and the underlying bone was covered with granulation tissue. It was felt that the infection had spread from the lateral wall of the right antrum up along the anterior portion of the lateral wall of the orbit. Staphylococcus albus (coagulase positive) was cultured from the pus. Following this operation there was again improvement, but he was transferred to Stanford Hospital when the pain and swelling recurred on December 20. The temperature was normal, but there was a definite protrusion of the right eye with eversion of the lower lid and conjunctivitis. A small abscess below the eye was drained and S. albus (coagulase positive) was again cultured. X-ray examination revealed cloudiness of the right antrum and ethmoids and both frontal sinuses. There were slight but definite osteomyelitic changes of the frontal bone in the region of the right temporal fossa, and pitting edema was noted over this area. A right intranasal antrotomy was performed, and penicillin was administered by the continuous intravenous route 200,000 units daily for eight days. Intramuscular injections of 15,000 units every three hours were then given for nineteen days, a total of 3,650,000 units by both routes. During this time the redness, pain and swelling disappeared altogether, although the proptosis remained and the x-ray changes persisted. After three weeks at home he returned on Feb. 15, 1944 with a corneal ulcer and diffuse conjunctivitis of the right eye, resulting from insufficient protection afforded by the everted lower lid. In addition to local treatment he received 840,000 units of pencillin intramuscularly over a period of a week. During a follow-up period of two months there has been no evidence of recurrence of infection, and the cornea has been protected by dark glasses and merthiolate ointment. A plastic repair of the lid will be performed at a later date.

CASE 4.—*Osteomyelitis of frontal bone and brain abscess following sinusitis; stormy course with convulsions and paralysis of the left arm and leg following surgical operation; cure with prolonged penicillin therapy and aspiration of a second brain abscess.*

During the second week of December 1943 J. C., a white man aged 51, developed acute frontal sinusitis with severe headache and photophobia. The pain became progressively worse in spite of chiropractic treatment, and a swelling of the soft tissues appeared above the right eye. A typical grand mal seizure on Jan. 12, 1944 prompted transfer to Stanford Hospital, where the patient was found to be semistuporous and had a temperature of 40.5 C. (104.9 F.). There was stiffness of the neck, but no abnormal reflexes were elicited. Pitting edema was noted over both eyebrows, especially on the right. The white blood cell count was 22,400 and the spinal fluid contained 1,000 cells per cubic millimeter, all polymorphonuclears. Both the blood and the spinal fluid were sterile at this time. A continuous intravenous infusion of penicillin was begun, 100 units per cubic centimeter, and at operation he was found to have right frontal sinusitis with osteomyelitis, extradural and subdural pus, and an abscess of the right frontal lobe. The affected bone was removed as completely as possible, and drains were placed in the abscess cavity. The whole area was irrigated with penicillin solution, and the wound was

covered with penicillin saturated gauze. Anaerobic nonhemolytic streptococci were cultured from the right frontal sinus and brain abscess. Postoperatively penicillin was administered by the continuous intravenous route 300,000 units daily for eight days, and the head wound was irrigated two or three times daily with penicillin 100 units per cubic centimeter. During this time the course was stormy, with continued high fever, clonic convulsions at frequent intervals, periods of Cheyne-Stokes respiration and a flaccid paralysis of the left arm and leg. On January 18 a few nonhemolytic streptococci were cultured from the spinal fluid, and the next day 10,000 units (1,000 units per cubic centimeter) of penicillin was instilled intraspinally. All other cultures of the spinal fluid were sterile. Penicillin was discontinued because of a generalized maculopapular erythematous rash, which appeared six days after therapy was instituted and became progressively worse. After fading promptly, the rash reappeared six days later, when 180,000 units of penicillin from the same manufacturer was administered intramuscularly in thirty-six hours. It again faded promptly and was apparently a dermatitis medicamentosa caused by a certain lot of penicillin. The patient remained disoriented and semicomatose and on February 2 passed into a deep coma, with irregular heart beat and respirations. Pus (8 cc.) was aspirated from a second brain abscess located posterior to the first in the prerolandic area; cultures again revealed anaerobic nonhemolytic streptococci. Penicillin 100 units per cubic centimeter was instilled into the cavity, and no pus was obtained when a second aspiration was attempted three days later. Since it seemed imperative, penicillin therapy was again started, preparations other than the preparation which had previously caused the rash being used, and this time there was no recurrence of dermatitis. The wound was irrigated three times a day with 5 and 10 cc. (100 units per cubic centimeter) and 15,000 units was injected intramuscularly every three hours. Beginning with the aspiration of the second brain abscess and the reinstitution of penicillin therapy there was slow but steady improvement. The spinal fluid, at first cloudy and under increased pressure, gradually cleared so that daily taps were no longer necessary. Convulsions ceased, the patient regained his mental faculties and the paralysis of the left arm and leg gradually disappeared. The exposed anterior pole of the right frontal lobe of the brain prolapsed through the wound at first and became covered with purulent granulations. As this tissue became necrotic it was gently wiped away with sterile gauze. The brain then gradually receded and for two weeks, from February 24 until March 9, a profuse leakage of cerebrospinal fluid occurred from the wound; this gradually decreased and ceased spontaneously. Penicillin was finally discontinued on March 16, two months after the patient was admitted to the hospital. At this time the wound was clean and epithelium was beginning to cover the healthy granulation tissue. Mentally there was complete recovery, and the left arm and leg had regained much of their original strength. The total amount of penicillin administered locally and parenterally was 7,540,000 units.

CASE 5.—*Osteomyelitis of frontal bone following surgical operation for frontal sinusitis; failure to respond to sulfonamides, with fever and bacteremia; prompt response to penicillin; sequestrectomy later with a second course of penicillin.*

E. A., a man aged 53, developed a swelling over the right eye in March 1943, which subsided in four days. In September the pain and swelling recurred and this time did not respond to conservative therapy. On October 21 in another hospital both frontal sinuses were opened widely and the anterior ethmoid cells removed. Two weeks later the patient developed a low grade fever, headaches and edema over the frontal bones. Subacute osteomyelitis was diagnosed, and the process continued to spread in spite of intensive therapy with sulfonamides. He entered Stanford Hospital Jan. 21, 1944 with a temperature of 38.5 C. (101.3 F.), pitting edema over the forehead and a draining sinus above the medial side of the right eye. Anaerobic nonhemolytic streptococci were cultured from the blood and from the draining sinus; S. aureus (coagulase positive) was also isolated from the latter site. The blood count was normal, but both the blood and the spinal fluid Wassermann reactions were positive. X-ray examination showed an extensive widespread, moth-eaten destruction of the frontal bone, most pronounced on the right. A continuous intravenous infusion of penicillin was started January 22, 200,000 units daily for twelve days, a total of 2,400,000 units. Intramuscular injections were then given, 15,000 units every three hours for a week, a total of 760,000 units. For the first eight days, penicillin (100 units per cubic centimeter) was also injected into the draining sinus, 4 to 10 cc. twice a day. During this time his temperature subsided to normal, headache disappeared and drainage ceased. He left the hospital but returned on February 29 for the removal of several large sequestrums of the frontal bone through an incision just above the right eyebrow. In conjunction with surgical operation intramuscular penicillin was again given, 120,000 units daily for fourteen days, a final total of 4,847,000 units for both entries. S. aureus (coagulase positive) was cultured from the sequestrums, and sections showed changes characteristic of chronic osteomyelitis with sequestration. The postoperative course was uneventful, but x-ray examination revealed that not all of the sequestrums had been removed. The wound is now healed and the patient is entirely well, but the follow-up period of six weeks is too short to be sure that there will be no further recurrences. The course of the asymptomatic neurosyphilis will also be followed with great interest.

COMMENT

The fundamental principles underlying the treatment of osteomyelitis of the facial bones are well illustrated by these 5 cases. In contrast to the sulfonamides, penicillin prevents further spread of the infection, so that either before or after sequestration has occurred devitalized bone can be removed surgically. Relapses are likely to occur until all the necrotic bone is gone. Surgical procedures are probably best postponed until the patient has had three or four weeks of penicillin therapy and sequestration has occurred, since there is then a better possibility of removing all the devitalized bone at one time.

Penicillin dosage is still controversial. The first 2 patients were given small amounts for only a few days, as a result of which there were frequent relapses. Prolonged treatment with larger doses prevented relapses in the other 3 cases and possibly shortened the course of the disease. The present policy in this clinic is to administer 200,000 units daily by continuous intravenous drip for ten days to two weeks, followed by 15,000 units intramuscularly every three hours (120,000 units daily) for another two or three weeks. If surgical treatment is delayed until sequestration has occurred, penicillin should be continued for at least a week postoperatively.

The only toxic reaction observed was a generalized maculopapular rash (case 4), which appeared six days after treatment was begun and faded promptly when penicillin was discontinued. The rash did not recur when the patient was given penicillin prepared by a different manufacturer.

In cases 1, 2, 4 and 5 anaerobic nonhemolytic streptococci were probably primarily responsible for the osteomyelitis, with S. aureus (coagulase positive) also present in cultures from sinuses communicating with the skin. These same organisms were isolated by Williams and Nichols,[1] who also report excellent results with penicillin. S. albus (coagulase positive) was the only organism recovered in case 3.

The results in these 5 cases would seem to justify the hope that the present high mortality rate in cases of acute, subacute and chronic osteomyelitis of the facial bones will be drastically reduced when supplies of penicillin become generally available.

1. Williams, H. L., and Nichols, D. R.: Spreading Osteomyelitis of the Frontal Bone Treated with Penicillin, Proc. Staff Meet., Mayo Clin. **18**: 467 (Dec. 1) 1943.

SUBACUTE BACTERIAL ENDOCARDITIS

INHERENT DIFFICULTIES IN PROGNOSIS; A REPORT OF TWO RECOVERIES AND TWO DEATHS

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Since the advent of sulfonamide therapy, a slowly increasing number of carefully studied patients who have recovered from subacute bacterial endocarditis have been the subject of reports. Patients living and well one year after treatment are considered recovered. The most discouraging report comes from Galbreath and Hull,[1] who had 42 deaths in 42 patients treated with sulfonamides. The experiences of Smith, Sauls and Stone [2] are more encouraging. They add two cures to the 35 authentic instances of recovery which they could find in the literature.

Several plans of treatment, all utilizing the sulfonamide drugs, have been described. Bierman and Baehr [3] report some successes with combined physically induced pyrexia and chemotherapy. I have used this method on 2 patients, both of whom died but not for several weeks after hypertherm treatment was discontinued. These 2 fatal cases are briefly summarized to illustrate the point that treatment was vigorous and yet of no avail.

FATAL CASES

CASE 1.—Mrs. M. C., aged 33, a private patient hospitalized June 7, 1941 in Youngstown Hospital, had rheumatic fever at the age of 10. Fourteen weeks before admission to the hospital she had several teeth removed. Her symptoms of fever, malaise and chilliness developed soon after this dental experience. Blood cultures were found positive for Streptococcus viridans on three different occasions. She was given sulfonamide drugs totaling 65 Gm. in a period of nine days. The blood sulfadiazine level was as high as 27.4 mg. per hundred cubic centimeters. During this period of high concentration of the drug in the blood, hypertherm treatments were given in the Kettering fever therapy cabinet. The body temperature was elevated 105 to 106 F. each day. The patient died at home approximately two months after the last treatment. There was a short remission of symptoms and signs for a period of one week following intensive treatment.

CASE 2.—M. M., a Negro girl aged 17, admitted to Youngstown Hospital, South Side Unit, Jan. 24, 1943 with the history of a previous admission at the age of 12 for treatment of rheumatic fever and endocarditis, had been examined in the heart clinic in 1941 because of "spitting of blood clots." X-ray examination of the lungs was negative at that time. Aortic and mitral diseases were present. She had an uneventful pregnancy and labor with a living child in March 1942. Three weeks before admission she was said to have had pneumonia. The provisional diagnosis on admission was subacute bacterial endocarditis. This was confirmed by the clinical course and five blood cultures positive for streptococcus viridans. During her four months in the hospital a total of 236.5 Gm. of sulfonamide drugs was given. The highest blood level was 19.3 mg. of sulfadiazine per hundred cubic centimeters. The patient was in the hypertherm cabinet ten times, the temperature each time varying between 105 and 106 F., for a total of nineteen and one-half hours. Five blood transfusions averaging 370 cc. were given by the indirect method. The patient died on May 10, 1943, twenty-four days after the last hypertherm treatment, with no evidence that treatment had influenced the course of the disease in any manner.

Orgain and Poston [4] stress the importance of preliminary in vitro experiments to determine the most effective drug and its optimal chemical level of inhibitory action.

In the report of Dick [5] the patient had an initial infection of his right hand, as did 1 of my patients. Dick gave 40 Gm. of sulfadiazine in one dose, a method which was found ineffective by Hull, Bayley and Holoubek.[6]

CASES WITH RECOVERY

I have had 2 cases of subacute bacterial endocarditis in the past three years in which recovery occurred. These 2 are reported together because of certain contrasts. The first record is of a man shown in person at the 1941 meeting of the American Heart Association in Cleveland. He had a definite rheumatic fever history and may be fairly classified as presenting a classic example of subacute bacterial endocarditis.

The second case had a much more abrupt onset and had as a predisposing factor a patent ductus arteriosus. This case is particularly interesting at the present time because of the possibility of preventing further attacks by tying off the patent ductus. Both cases were treated with sulfonamide therapy, one with moderate doses over a long period of time and the other with larger doses given intravenously for seven weeks. Both of these patients are living and have been at work for more than one year.

CASE 3.—F. W. B., a man aged 47, was first examined in 1934, when he observed that he was too tired after his usual tennis game. No enlargement of the heart and a soft diastolic aortic murmur were recorded at that time. On the basis of a history of a severe attack of rheumatic fever with "dropsy" and a "murmur" at the age of 12, the diagnosis of chronic rheumatic valvulitis was made. The patient was instructed to reduce his physical activities; this restriction he accepted. He was urged to use less nicotine than two packs of cigarets a day; this advice he did not accept. He was comfortable until 1936, when he had a stormy painful seizure of renal colic and passed a small calculus. In 1936 he had an appendectomy with uneventful recovery. There were no signs of increase in the pathologic condition of the heart noted at that time.

In October 1939 he developed a painful fibrositis and tenosynovitis in his left forearm. He had not completely recovered from this illness when on a stormy week end he took a 400 mile automobile trip to a football game. He "caught cold" and developed precordial pain, which, though not severe, was persistent and annoying. From this time on he was "too tired all the time." He was not seen by a physician until February 1940, when he developed an upper respiratory infection during the unusually cold weather in Florida, where he had gone "to try to get strong." He was quite ill for two weeks and then "not well enough to get around" until he came north in May. He entered a hospital in Cleveland, where the diagnosis of subacute bacterial endocarditis was made and confirmed by three blood cultures positive for Streptococcus viridans.

On May 21, 1940 he came under my care with all the classic signs of subacute bacterial endocarditis. He was given sulfa-

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5. Dick, G. F.: Subacute Bacterial Endocarditis: Recovery Following Intravenous Sodium Sulfadiazine, J. A. M. A. **120**: 24-25 (Sept. 5) 1942.
6. Hull, E.; Bayley, R. H., and Holoubek, A. B.: Therapy of Bacterial Endocarditis with Massive Dosage of Sulfadiazine: Report of Four Cases, J. A. M. A. **122**: 928-930 (July 31) 1943.

thiazole, which at that time was obtainable only for investigational use. This preparation, furnished gratis by Merck & Co., was administered by mouth in gradually increasing doses up to 7.5 Gm. daily for one month. Fourteen days of this month were spent in the hospital. The drug was discontinued on June 21, 1940 for a period because of hematuria. A total of 41 Gm. had been ingested up to that time. The details of the pulse, temperature, white blood count, sulfathiazole blood level and daily amount of sulfathiazole given during his hospital stay are shown in figure 1. In addition to leukocytosis, elevated temperature and rapid pulse the patient had a tender spleen, splinter hemorrhages under the nails and evidences of emboli on the trunk and extremities. The aortic diastolic murmur recorded first in 1934 was of the same quality as noted at that time. Precordial pain was a troublesome symptom. No friction rub was heard, but the character and distribution of the pain suggested an acute pericarditis.

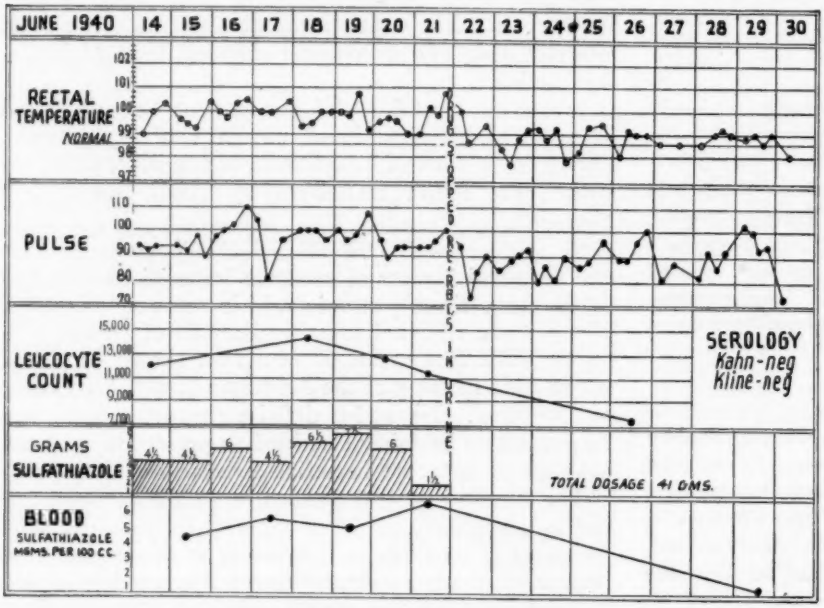

Fig. 1.—Pertinent data in case 3.

The patient was in bed all of May and June 1940. He returned to work Aug. 15, 1940 and has been actively engaged as an executive since that time. During this past busy season he has worked overtime almost every day. On his own initiative he took a daily dose of at least 1 Gm. of sulfathiazole for one year following his illness. He was readmitted to the hospital in 1941 for cardiovascular examination. His heart had changed but little in size since the original examination in 1934. The aortic diastolic murmur was of the same quality, but a mitral systolic murmur was heard at the apex of the heart. This was not present during his illness of 1940. It is, I believe, clear evidence of a mitral valvulitis which developed during his septicemia.

Case 4.[7]—I. T., a woman aged 21, a worker in a glass factory, was noted by the examining physician as having a "heart murmur" at the time she was hired in 1941. She had been told in early childhood that she had "heart trouble." In spite of warnings by family and physician, she had engaged in more strenuous activities than the average youngster. During her school years she had been one of the best players on a girls' baseball team and had never noted loss of cardiac reserve. She had no history of having had rheumatic fever, chorea, scarlet fever or any disease which might have been interpreted as a rheumatic manifestation.

On Feb. 6, 1942 she reported to the plant dispensary because of two furuncles on the inner side of the right forearm and a moderately diffuse swelling of the right palm, most prominent at the base of the second finger. She was given x-ray treatment of 100 roentgens over the infected areas.

On February 7, because of a moderate lymphadenitis, the palmar infection was opened and a very small amount of thick creamy pus was obtained from just under the skin. All local signs of infection promptly subsided. The temperature and pulse, which had been slightly elevated, returned to normal.

On February 16 she had a temperature of 101 F. There was tenderness over one gland in the right axilla. She had two doses of sulfathiazole but refused to take more because of nausea. Because of the persistence of fever, sulfathiazole was again administered from February 24 to March 3, a total of 18.5 Gm. being ingested during this period.

The patient was admitted to the City Hospital in Warren, Ohio, on March 4, 1942 with a provisional diagnosis of septicemia. Her temperature on the evening of admission was 101.8 F. and the pulse rate 114. On the next day the white blood cell count was 3,900, hemoglobin 60 per cent and red blood cell count 3,840,000. The blood culture on March 6 (two days after admission) was positive for streptococcus. Positive cultures were obtained on March 6, March 7 and March 9. All of these were subcultured and found to be Streptococcus viridans.

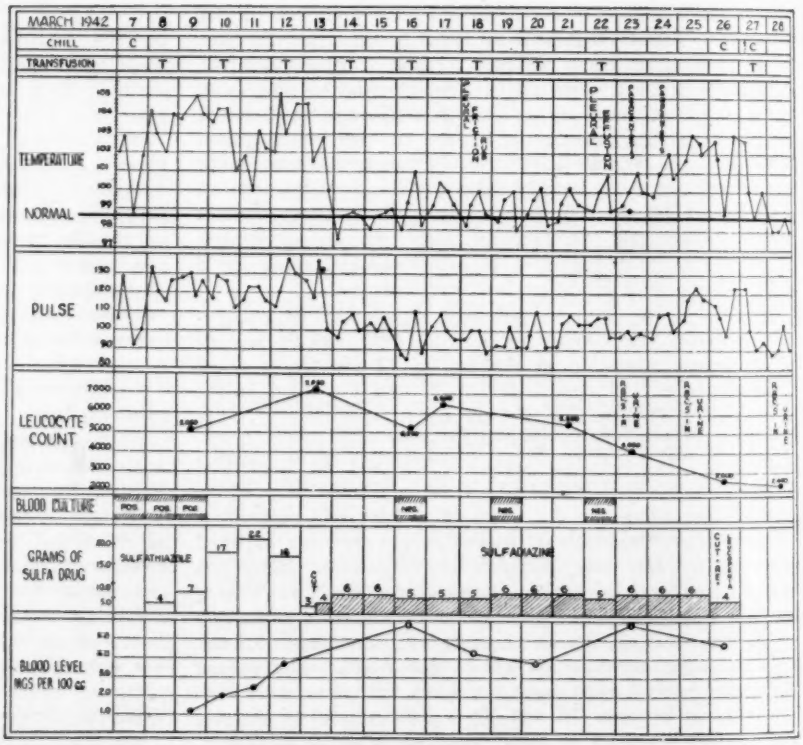

Fig. 2.—Details of treatment and response in case 4.

7. Dr. Paul Gauchat of Warren, Ohio, gave me permission to report this case, which I saw in consultation several times in March 1942. Dr. Gauchat made the x-ray studies and carried the burden of the routine treatment.

On March 7 the patient had a chill. The temperature was 103.8 F. A record of the clinical course and treatment during the period of the most serious illness (March 7 to March 28) is shown in figure 2.

Sulfathiazole therapy was resumed on March 8, but the patient was unable to retain it because of nausea and vomiting. Large doses of sodium sulfathiazole were then given intravenously beginning March 9.

Repeated small blood transfusions seemed indicated on account of the severe anemia present on admission and because favorable clinical effects were noted following transfusions during the most critical period of the illness.

Because of severe dehydration, liberal quantities of fluid, as much as 6,000 cc. in twenty-four hours, were given orally and parenterally. This may be one reason for the lack of high concentration of sulfathiazole in the blood, for at no time did this exceed 6 mg. per hundred cubic centimeters. There was another factor influencing the blood sulfathiazole level. The patient had exceedingly small veins, so that there was considerable mechanical difficulty in giving fluids and obtaining specimens of blood for tests. The plan evolved was to take the blood specimen for laboratory purpose through the same needle through which the drug was given, but just before sodium sulfathiazole was injected. This meant that the test was taken twelve hours at least after the time when the highest concentration of the drug might have been expected in the blood.

There were two crops of petechial hemorrhages involving both feet on March 10, and multiple petechiae appeared on the hands and feet on March 12.

Because of persistent and repeated emesis, sulfathiazole was discontinued on March 13, and the patient was given sulfadiazine by mouth.

On March 18 the patient developed a pleural friction rub at the base of the right lung. This radiated to the right shoulder. There was clinical and x-ray evidence of considerable effusion in the right pleural cavity with a fluid level at the seventh rib. On March 23, 50 cc. of straw colored fluid for diagnostic purposes was removed from the right pleural cavity.

There was a palpable inguinal gland noted on March 26, and phlebitis of the veins of the left calf appeared the next day. Both of these complications subsided promptly and completely.

General clinical improvement was evident on March 26. At this time a disturbing leukopenia developed, and sulfadiazine was discontinued. The temperature became normal on March 28, and from then on recovery was uneventful.

During the period of her highest temperature, most rapid pulse rate and greatest toxemia it was my impression that the murmur at the base of the heart and at the apex changed in quality, the typical murmur of patent ductus arteriosus being harsher and more easily heard than on first examination and the systolic murmur at the apex much louder and more prolonged.

The patient left the hospital on May 16, 1942, two months and twelve days after admission. She felt well and was strong enough to walk about. There were no clinical signs other than the persistence of the continuous machinery-like murmur of patent ductus arteriosus at the base, and the soft systolic apical murmur. The electrocardiogram showed no significant departure from normal. The blood pressure was 120 systolic and 80 diastolic, the pulse rate 78 and the cardiac rhythm normal.

One year ago the patient was able to return to work (Aug. 3, 1942). To date there has been only one interruption of her normal life and that was due to a sharp attack of pyelitis on Sept. 25, 1942, which caused chills and high fever for three days and kept her from work for one week. Her chief worry at the present time is her excessive gain in weight.

COMMENT

No explanation can be given at this time for the beneficial effects of sulfonamides in the recovered patients, when 12 other cases treated during the same period have failed to be influenced in the least by similar or more intensive treatment.

One very sound reason for not being too optimistic about the cure of subacute bacterial endocarditis with sulfonamide compounds or any other substance is autopsy experience. When hearts such as the one

Fig. 3.—Heart of patient dying of subacute bacterial endocarditis. Note large left atrial mural thrombus. Destruction of mitral valve by vegetation.

shown in figure 3 are studied, the futility of treatment in similar cases must be acknowledged. Large adherent mural thrombi and multiple valve vegetation, such as those shown here, constitute depots of continuous infection which no known treatment can conceivably conquer.

In the authentic cases of recovery reported probably there was little structural damage and the infection was due to a type of streptococcus which had low resistance to the sulfonamide drugs. Our inability to recognize in advance the incurable cases makes it obligatory to treat vigorously all patients having subacute bacterial endocarditis with one of the sulfonamide drugs. Though few, these favorable results enable us to offer some hope to those who heretofore had no chance for recovery.

603 Home Savings & Loan Building.

First Accurate Medical Historian.—Thucydides (471-400 B. C.) is the first accurate medical historian. His description of the plague at Athens is, he tells us, that of an eye witness. As you study it, ask yourself the question "How would I describe an epidemic that was new and strange and struck my own city? What facts would I record and in what order?" Then notice how completely Thucydides covers the ground. In spite of the careful description of the signs and symptoms, however, it is not possible to identify positively Thucydides' plague. W. H. S. Jones thought it was malaria. More likely it was bubonic plague. The ancient and medieval world was the stage for many destructive epidemics. Both bubonic plague and influenza cause intense cyanosis, so either could have been "the black death." After Thucydides, the great plagues were (1) that following the eruption of Vesuvius, A. D. 79, which destroyed Pompeii; (2) the plague of Orosius, A. D. 125, preceded by an invasion of grasshoppers which spread over Italy and northern Africa, Carthage and Utica; (3) the plague of Antoninus, A. D. 164-180, all over the Roman Empire; (4) the pestilence of Cyprian, A. D. 251-266, probably smallpox; (5) the black death appeared in Europe about 1348, and repeated its visitations too often to mention.—Clendening, Logan: Source Book of Medical History, New York, Paul B. Hoeber, Inc., 1942.

A PANORAMIC VIEW OF THYROTOXICOSIS

REGINALD FITZ, M.D.
BOSTON

(Concluded from page 947)

POST-THERAPEUTIC HYPOTHYROIDISM

Table 4 summarizes results which developed in 5 cases in which treatment directed to the thyroid gland appeared to result in the fairly prompt development of perceptible hypothyroidism. As a rule, postoperative hypothyroidism became manifest within a comparatively short time and thyroid was helpful in therapy. But none of the patients claimed to feel as well after developing hypothyroidism as when they were normal, so that, on the whole, the development of hypothyroidism as a complication of thyrotoxicosis was by no means a fortunate occurrence.

This impression is of some interest. Such surgeons as Poate and Wyndham,[19] Dobson, Seely and Rose,[20] Berlin and Gargill [21] and Albright and Clute,[22] who have reported recently on the end results in thyroid surgery, have encountered postoperative hypothyroidism in a certain proportion of their cases and seem to make but little of it. Indeed a truly radical surgeon like Scott [23] appears to advocate so total a subtotal thyroidectomy in his most toxic cases as seemingly to aim for postoperative hypothyroidism.

TABLE 4.—*Development of Hypothyroidism in Patients Treated for Hyperthyroidism*

Case No.	Treatment of Hyperthyroidism	Date of Present Note	Comment
1	Irradiation	4 years later	Basal metabolic rate —19 two years after; now fairly comfortable on thyroid
18	Subtotal thyroidectomy	15 years later	Feels cold, tires easily and has poor memory; fairly comfortable with thyroid; basal metabolic rate —18
26	Subtotal thyroidectomy (thyrocardiac)	6 years later	Hypothyroidism recognized six years after operation; fairly comfortable with thyroid; weight now 73.5 Kg.
27	Subtotal thyroidectomy	12 years later	Hypothyroidism recognized a year after operation; manages to be fairly comfortable with judicious use of thyroid
30	Subtotal thyroidectomy	7 years later	Hypothyroidism recognized a year after operation; takes thyroid regularly and feels fairly well but always less than normally energetic and active

Even those patients reported in table 3 who apparently obtained excellent results from therapy are not all entirely happy, since the ones who have gained so much weight as to become obese are not normal individuals; they admit that they are never perfectly well, are less efficient than they were before they became ill and claim to find it unduly hard to lose weight by diet restriction. Those who are hypothyroid are even more conscious of their liabilities; unenergetic, sluggish, perhaps having found it difficult to bear normal children, and in general almost as much handicapped by being forced to rely on thyroid as is the diabetic patient who has to rely on insulin.

The duration and true significance of hypothyroidism developing as the result of treatment in thyrotoxicosis is difficult to appraise because many bizarre happenings may occur in connection with it. For example, Wilson and Mayo [24] saw 2 cases of clinical postoperative myxedema that later became hyperthyroid. Haines's [25] and Zondek's [26] cases are very similar. Not long ago, however, I saw a patient who gave me much food for thought:

B. M. developed the clinical picture of thyrotoxicosis when she was 28 years old. She then had a subtotal thyroidectomy; her basal metabolic rate was +69 and, according to the pathologic report of Dr. Shields Warren at the time, the gland showed primary hyperplasia with a moderate degree of strumitis.

She felt very well for several years after the operation except that she developed gallstones, which were treated successfully. I first saw her twelve years after her thyroidectomy, through the courtesy of Dr. Howard M. Clute. She had gained a great deal of weight and now looked like a person with hypothyroidism. Her basal metabolic rate had fallen to —18, and the blood cholesterol was 230 mg. per hundred cubic centimeters. She was advised to take thyroid and to diet carefully in order to lose weight.

For the ensuing four years she felt well, never bothering, however, to take thyroid regularly. Then she began to notice that she was becoming hoarse and was losing all her energy. Finally she returned to me for examination, nineteen years after operation. She had a basal metabolic rate of —37 and gave every appearance of myxedema.

I described her predicament to Dr. Warren and asked him to review her thyroid sections. He says that, in light of present knowledge, he believes it would have been possible to prophesy from the way her thyroid gland looked when he studied a section from it nineteen years ago that she was likely to develop myxedema if she lived long enough. For now he suspects that she had from the beginning a pathologic condition more like the early stages of that peculiar form of thyroid disease called struma lymphomatosa than ordinary toxic diffuse goiter.

In the literature have been reported other hints such as this which suggest that the experienced pathologist of today, if he had the chance, could spot for his surgical colleagues at the operating table those patients particularly liable to develop hypothyroidism after partial thyroid ablation. Plummer and Boothby,[27] for instance, before the days of iodine felt reasonably certain that the incidence of postoperative myxedema in thyrotoxicosis was more or less proportional to the degree of lymphocytic infiltration and fibrosis which happened to be present in the thyroid gland at the time of operation. It is not impossible, therefore, that preoperative biopsy with careful study of the thyroid gland before any more radical operation might be of material help in guiding treatment. Certainly the prevention of post-therapeutic hypothyroidism would be a distinc. advance in the treatment of thyrotoxicosis.

19. Poate, H. R. G., and Wyndham, N. R.: The End Results of the Surgical Treatment of Thyrotoxicosis, M. J. Australia **1**: 505-509 (April 13) 1940.
20. Dobson, L.; Seely, H., and Rose, H., Jr.: The End Results of Thyroidectomy, Ann. Surg. **115**: 199-205 (Feb.) 1942.
21. Berlin, D. D., and Gargill, S. L.: Factors Influencing Persistent and Recurrent Hyperthyroidism, New England J. Med. **222**: 254-259 (Feb. 15) 1940.
22. Albright, H. L., and Clute, H. M.: Six Years' Experience of the Thyroid Service at the Massachusetts Memorial Hospitals, New England J. Med. **227**: 363-370 Sept. 3) 1942.
23. Scott, A. C.: The Surgery of Recurrent Exophthalmic Goiter, Texas State J. Med. **32**: 649-652 (Feb.) 1937.
24. Wilson, W. D., and Mayo, C. W.: Postoperative Myxedema, Surgery **7**: 117-121 (Jan.) 1940.
25. Haines, S. F.: Exophthalmic Goiter Developing in a Case of Postoperative Myxedema, Proc. Staff Meet., Mayo Clin. **5**: 48-49 (Feb. 19) 1930.
26. Zondek, H.: Graves' Disease—Myxoedema—Graves' Disease, Lancet **1**: 75 (Jan. 16) 1943.
27. Boothby, W. M., and Plummer, W. A.: Diseases of the Thyroid Gland, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 3, pt. 3, p. 904.

RECURRENT TOXIC GOITER

Table 5 summarizes the results in 3 cases with true recurrences necessitating operative treatment. It is interesting that in 1 instance no appreciable recurrence occurred until seven years after thyrotoxicosis was first recognized and treated by surgical means. This is not unusual, and one can easily assemble curious stories along this line. A certain woman now 57 years old was operated on for hyperthyroidism in 1913, thirty-one years ago. She did well for eleven years, until 1924, when she had a recurrence with a second operation. Eight months later she had a third recurrence, which also was treated by surgery. The disease then was quiescent for eight years. But in 1932 a fourth recurrence developed, and since then her thyroid gland appears to have behaved itself.

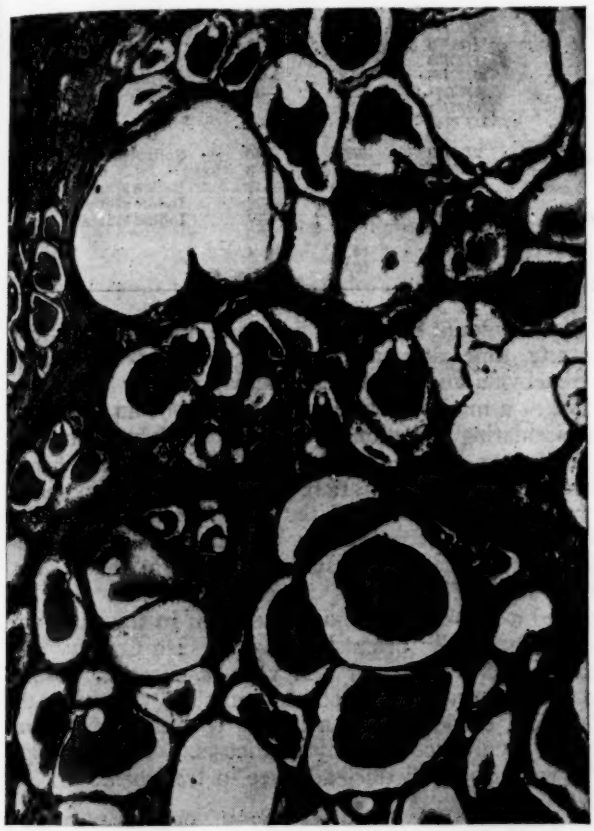

Fig. 2.—End result on the thyroid gland of thyrotoxicosis treated by surgery: Section of the same thyroid gland that was shown in figure 1 obtained at necropsy ten years later. The remnant weighed 11 Gm. The acini are dilated. The epithelium is low cuboidal. There is considerable increase in connective tissue. The gland appears atrophic rather than hyperplastic. Reduced from a photomicrograph with a magnification of 50 diameters. (Courtesy of Drs. Shields Warren and S. B. Wolbach.)

The frequency with which recurrences develop after any form of treatment varies but is always a sore point. Coller and Potter [28] have described the situation clearly; in light of present knowledge thyrotoxicosis, they admit, is due to an unknown exciting cause. The surgical approach is to interrupt a vicious circle through an attack on hyperactivity of the thyroid gland, this being one known factor in the circle. No measured amount of thyroid tissue always to be exactly proper can possibly be left behind after subtotal thyroidectomy: if too much is taken out, hypothyroidism will probably develop, and if too little, recurrence of the clinical picture is likely. To an internist the line between the production of artificial myxedema and failure to check hyperthyroidism is a fine one; the wonder is that satisfactory results from surgery are obtained as frequently as they are.

Rienhoff [14] made biopsies of thyroid glands from patients operated on for thyrotoxicosis at intervals after operation. His studies suggested that subtotal thyroidectomy did not diminish histologic evidence of thyroid hyperplasia up to several months after operation. Branch [29] has had opportunity to examine the thyroid remnant in 1 case eight weeks after subtotal thyroidectomy for thyrotoxicosis. His findings confirm Rienhoff's. He reports that the appearance of the two sections were much alike. in the one was evidence of a hyperplastic overactive gland which came from a patient known to have an elevated metabolic rate; in the other was evidence of a hyperplastic overactive gland in a thyroid remnant weighing only a few grams, also known to come from the same patient, now with normal metabolic rate. Such evidence suggests, therefore, that the thyroid remnant after operation continues to be stimulated by whatever the fundamental cause of the disease may be and does its best to produce thyroxine as fast as it can until possibly Barker's "burning out" process becomes manifest or until one of Plummer's cycles of spontaneous remission occurs.

TABLE 5.—*Cases with Recurrent Thyrotoxicosis*

Case No.	Treatment of Hyperthyroidism	Date of Present Note	Comment
2	Subtotal thyroidectomy	8 years later	Developed recurrence three years after first operation; had second operation and developed hypothyroidism; death eight years after first operation
19	Subtotal thyroidectomy	24 years later	Developed recurrence two years after first operation and a third recurrence three years after the second; both recurrences were treated by surgery; since last operation has enjoyed good health
31	Subtotal thyroidectomy	19 years later	Developed recurrence seven years after first operation and a third recurrence two years after the second; both recurrences were treated by surgery; since last operation believes that she has had waves of minor recurrences controlled by iodine and rest; has gained 30 Kg. since first operation

Rienhoff's findings coupled with other of his studies concerning the effect of thyroid on the microscopic appearance of the thyroid gland led him to resurrect an old idea: the use of thyroid in the treatment of hyperthyroidism. Fifty years ago this was a fairly popular form of therapy. At the annual meeting of the Massachusetts Medical Society in 1895, J. J. Putnam [30] spoke about modern views on the nature of toxic diffuse goiter. In discussing treatment he announced it was known that occasionally the use of thyroid led to an improvement in the condition, and this was indeed a blow to those who thought that the disease was related to excessive thyroid secretion.

Owen [31] was one of the early proponents of thyroid feeding in the treatment of thyrotoxicosis. In 1893 he reported a most striking case: A man with hyperthyroidism was advised to eat each day one fourth lobe of freshly minced sheep's thyroid flavored with a little salt and vinegar. Once, by mistake, for two days

28. Coller, F. A., and Potter, E. B.: The End Results of Thyroidectomy, Ann. Surg. **94:** 568-581 (Oct.) 1931.

29. Branch, C. F.: Personal communication to the author.

30. Putnam, J. J.: Modern Views on the Nature and Treatment of Exophthalmic Goitre, Boston M. & S. J. **133:** 131-137 (Aug. 8) 1895.

31. Owen, D.: Thyroid Feeding in Exophthalmic Goitre, Brit. M. J. **2:** 1211 (Dec. 2) 1893.

the man's wife gave him one-fourth pound of this mixture to eat and this promptly induced what was described as a violent dyspepsia. A few days later the proper dosage was resumed and the patient was much gratified; for he steadily improved and finally grew well. Thus he continued with the medicine, finding that if he did not take it he would relapse, whereas so long as he used it he stayed in good trim.

A little over a year later Owen [32] made an interesting confession. A friend of his had read the first report and pointed out that the thyroid gland of a sheep ordinarily weighs 80 grains (5 Gm.), so that a quarter pound of sheep's thyroid would mean twenty whole glands a day and this appeared an incredible quantity for a man to ingest. Owen, therefore, examined what his patient was eating and discovered he had been taking thymus, an excusable mistake, in Owen's opinion, since the butchers of the day were familiar with the "neck-berg" and the "heart-berg" of young sheep (the cervical and thoracic thymus) but often were ignorant of the existence of the thyroid gland.

At about the same time Mikulicz [33] in Germany and Cunningham [34] in America reported that in the treatment of toxic diffuse goiter the use of minced thymus

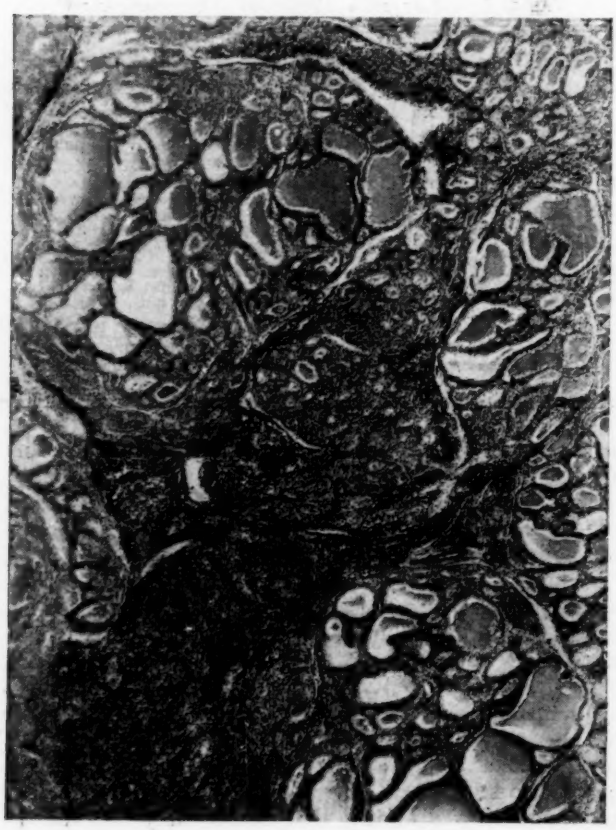

Fig. 3.—A type of hyperplastic goiter resulting in myxedema. The photograph is from a section of thyroid gland removed when the patient's metabolic rate was + 69. There is evidence of hyperplasia, but also there is considerable fibrosis and lymphocytic infiltration. Nineteen years later the patient's metabolic rate was — 37 and she had clinical myxedema. (Courtesy of Dr. Shields Warren.)

might be followed by results that were both surprising and pleasing. When one recalls how iodine first happened to be used by accident and was then discarded in the treatment of toxic diffuse goiter until H. S. Plummer reclaimed it, one feels that some modern investigator might do well to repeat Owen's work.

This, however, is by the way. For Rienhoff determined to use thyroid in the treatment of hyperthyroidism for an entirely different reason. He concluded

TABLE 6.—*Periodic Basal Metabolic Rate Determinations in Three Patients with Thyrotoxicosis*

Case No.	Date	Weight, Kg.	Basal Metabolic Rate	Comment
3	10/ 1/31	62.7	+38	Subtotal thyroidectomy
	10/18/32	75.0	— 6	
	2/11/35	72.7	—12	
	10/13/37	67.7	—21	
	12/16/38	70.3	— 7	
	11/12/40	67.7	— 9	
	10/ 7/42	69.0	—12	
	3/25/43	66.7	—10	
	1/19/44	69.0	—12	
25	9/16/37	72.3	+30	Subtotal thyroidectomy
	4/11/38	69.0	— 1	
	11/25/38	70.0	— 3	
	10/22/40	72.7	—27	
	4/30/41	....	—10	
	6/21/41	73.0	+ 8	
	11/ 6/43	73.5	+ 7	
21	2/ 1/39	51.7	+46	Subtotal thyroidectomy
	4/24/39	....	+ 6	
	9/ 5/41	60.0	+17	Iodine started
	10/16/41	....	+10	Iodine stopped
	2/10/42	....	+17	Iodine started
	5/ 4/42	....	+10	
	5/12/43	61.7	+ 4	
	2/10/44	60.9	— 8	

that the amount of thyroid secretion in the blood stream at any time determines the activity of the thyroid parenchyma and hence that cellular activity would take place at a minimum rate when there was an abundance of circulating secretion. With this thought in mind he first began to give thyroid to patients with hyperthyroidism after operation, thereby hoping to induce atrophy in the stump of tissue remaining and thus to do away with recurrences. So far he has noticed no detrimental effects from using thyroid in this fashion, and indeed his results appear promising. He has treated a few cases without operation in the same way and with equally promising results. De Courcy [35] has followed this lead and also reports success. It may be that by reviving an obsolete method we are on the threshold of developing a means to lessen post-therapeutic recurrences of thyrotoxicosis. To accomplish this would be a distinct advance in treatment.

THE PERIODIC EXAMINATION OF PATIENTS WITH TOXIC GOITER

One feature of thyrotoxicosis is very clear: patients with it must be carefully followed. Their periodic examination is fully as important as is the periodic examination of the diabetic, the cardiac or the syphilitic patient. Their weight must be watched, their level of metabolism must be surveyed at intervals, and unexpected complications must be guarded against as long as they live.

Table 6 reports the results in 3 patients who have been particularly cooperative in reporting whenever they were asked to; their records show apparent minor fluctuations in thyroid activity that might have been overlooked had they not been searched for. Patients 3 and 25 at one time appeared to be on the way to develop postoperative hypothyroidism. Whether this ever would have been at all significant is uncertain, because both took thyroid for a short time. Now, as the distance

32. Owen, D.: Further Notes on the Treatment of a Case of Exophthalmic Goitre, Brit. M. J. **1**: 361-362 (Feb. 16) 1895.
33. Mikulicz, J.: Ueber Thymusfütterung bei Kropf und Basedow'scher Krankheit, Berl. klin. Wchnschr. **32**: 342-346 (April 22) 1895.
34. Cunningham, R. H.: The Administration of Thymus in Exophthalmic Goitre, M. Rec. **47**: 742-745 (June 15) 1895.

35. De Courcy, J. L.: Prevention of Recurrent Hyperthyroidism, Ohio State M. J. **38**: 449-451 (May) 1942.

from operation lengthens, their metabolic rates appear stabilized. Patient 20 appeared to be headed in the direction of a recurrence. When her metabolic rate was found to be + 17 she felt nervous and out of sorts. She took Lugol's solution until the rate fell to + 10 and she felt better. The iodine was then discontinued, but a few weeks later the metabolic rate had risen to + 17 and subjectively she felt as she did before. Since then she has been taking iodine intermittently and her metabolic rate appears to be falling. It is difficult to feel at all sure that such minor changes mean anything; they are reported, however, to illustrate part of the interest that the reexamination of patients with thyrotoxicosis affords any one with clinical curiosity.

LESS COMMON SEQUELAE OF TOXIC GOITER

The remaining 3 patients each presented certain atypical features of thyrotoxicosis which fit in no grouping and must be considered individually:

Patient 6 was first seen when she was 46 years old. A few years later she developed diabetes and, on top of this, thyrotoxicosis when she was 59. Subtotal thyroidectomy was performed and now at 72 she has a basal metabolic rate of + 11, so that from the point of view of thyrotoxicosis she is well.

She is unwilling to pay any serious attention to her diabetes, which still exists. It is impossible to judge what effect, if any, the thyroid operation has played in relation to her other disease.

Patient 7 was first examined when she was 44 years old, a thin woman, hard working and seemingly an even tempered, well balanced individual. She was examined at yearly intervals for the following eight years. During the ninth she developed manifestations of thyrotoxicosis, which were treated by subtotal thyroidectomy. She recovered satisfactorily and appeared to be well for a year. Then suddenly she developed a psychosis of the manic-depressive type and for the last two years has required institutional care.

Fig. 4.—Immediate effect on the thyroid gland of thyrotoxicosis treated by surgery. Section of gland removed at operation reduced from a photomicrograph with a magnification of 70 diameters. The thyroid tissue removed weighed 54 Gm. The gland is diffusely hyperplastic. There is epithelial hyperplasia with the formation of papillary projections and slight lymphocytic infiltration.

A great deal has been written concerning this sort of occurrence, which unfortunately is not rare. The upshot of opinion by such psychiatrists as Katzenelbogen and Luton,[36] Dunlap and Moersch[37] and Rulison, White and Stalker[38] is that no particular type of psychosis is specifically associated with thyrotoxicosis. In certain instances hyperthyroidism may appear to play a part as an aggravating or precipitating factor in mental disease but, on the other hand, it may not. One is left with the impression that whatever relationship there may be between thyrotoxicosis and psychiatry is still undetermined.

Fig. 5.—Section of the same gland as shown in figure 4 obtained at necropsy eight weeks later. The remnant weighed only a few grams. It is diffusely hyperplastic. There is epithelial hyperplasia with the formation of papillary projections, and moderate lymphocytic infiltration with formation of secondary follicles. On the whole, the appearance of the two sections is much alike. (Courtesy of Dr. C. F. Branch.)

Patient 15 developed thyrotoxicosis at about the time of the menopause seven years ago, and ever since, despite subtotal thyroidectomy, has had a persistently elevated basal metabolic rate with a tendency to progressive exophthalmos.

Cases of this sort have perplexed many people. Lahey,[39] who has continued firmly to advocate the surgical treatment of thyrotoxicosis, believes that the postoperative continuance of hyperthyroidism indicates a left behind segment of hyperfunctioning gland. In such cases, he claims, the administration of iodine is unlikely to be of use, while the removal of a large portion of the segment is often needed to bring about a satisfactory result. Means, Hertz and Williams[40] have described what they term Graves' disease with dissociation of thyrotoxicosis and ophthalmopathy. They believe that there are cases in which eye manifestations are independent of the thyroid and that in such instances operation on the thyroid may be not indicated while full iodinization is. No doubt between these two extremes are borderline cases in which expert judgment in choice of treatment is imperative and decision is

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37. Dunlap, H. F., and Moersch, F. P.: Psychic Manifestations Associated with Hyperthyroidism, Am. J. Psychiat. **91:** 1215-1238 (May) 1935.
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39. Lahey, F. H.: Persistent and Recurrent Hyperthyroidism, Ann. Surg. **83:** 199-205 (Feb.) 1926.
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difficult. Cattell and Morgan [41] have advised a sensible middle course in doubtful cases. They assume that persistence of hyperthyroidism after operation is due to combinations of whatever factors outside the thyroid were responsible for the original difficulty, and they advise further surgery only for those who do not improve under medical treatment, seeming reluctant to advise reoperation until it becomes clearly indicated.

CHANGING VIEWS ON THE TREATMENT OF TOXIC GOITER

The literature on toxic goiter has a cyclic character which is most interesting. When thyrotoxicosis first became recognized, the thyroid gland was considered chiefly at fault and efforts were made to control its hyperactivity mechanically. As experience grew, an increasing number of investigators became convinced that thyroid hyperactivity was but a link in the disease, and, as knowledge of endocrinology advanced, the part that the thyrotropic hormone of the anterior pituitary played in producing the clinical picture of thyrotoxicosis came to the front. All this has been reflected in ideas on treatment. The experience of the Massachusetts General Hospital [42] shows that between 1919 and 1921 half the cases were treated by nonsurgical methods. Between 1932 and 1935 surgery was employed in almost every case. In 1942 half surgical and half nonsurgical procedures were employed, the nonsurgical cases including the special ophthalmopathic type in which Means, Hertz and Williams believe surgery is contraindicated and a variety of others treated successfully by iodine alone or by radioactive iodine and by x-rays. The recent discovery of thiouracil [43] as a depressant of thyroid function will undoubtedly stimulate further efforts at the treatment of thyrotoxicosis by other than surgical means.

Many years ago W. J. Mayo [44] spoke about the crudity of thyroidectomy and expressed the belief that when toxic goiter was better understood a less destructive method of treatment would come about. Little by little we are approaching its development.

SUMMARY AND CONCLUSIONS

Through an attempt to describe thyrotoxicosis as an actual experience in the life cycle of a group of patients observed over a long period of time, certain impressions have resulted which are clearcut and definite. They are by no means novel but serve to reemphasize the peculiar clinical course of a strange pathologic entity of unknown origin.

Hyperthyroidism, whatever its cause, is likely to be a serious affliction. It may affect any one of any age and either sex. It is found more frequently in women than in men. An individual who is tall or short, fat or thin, old or young may develop it, so that to speak of "Graves' constitution" is not altogether reasonable.

The early clinical recognition of hyperthyroidism is difficult. The patient developing it is at first stimulated and may feel unusually well. Only after thyrotoxicosis exists for some time so as to wear a patient down or unless it is notably acute does it make any one feel ill enough to seek medical advice, and by this time usually the diagnosis is easy.

The operative treatment of toxic goiter in expert hands is surprisingly successful. It is a time saving procedure and without great risk. On the whole, it is a more satisfactory form of treatment than any other so far developed. There are two complications following operation, however, which are so frequently encountered as to be a definite hazard: the development of postoperative hypothyroidism or of subsequent recurrences of hyperthyroidism. Both are serious. It is possible that modern methods of treatment and closer cooperation between the surgeon and the pathologist may help to avoid both of these complications in future.

The ultimate result of the surgical treatment of thyrotoxicosis is uncertain. In two completed cases reported here the thyroid gland did not show evidence of regeneration but was atrophic. More information on the entire course of toxic goiter is needed.

The patient with toxic goiter must be reexamined periodically as long as he lives. This is important because the disease naturally has a wavelike character and is chronic. Through careful periodic reexamination complications of toxic goiter may be recognized early, treated promptly, and the life of patients with it may be made more secure. Operative treatment interrupts a vicious circle through an attack on hyperactivity of the thyroid gland. It does not reach the fundamental cause of the disorder and thus is not a curative procedure.

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44. Christian, H. A.: Personal communication to the author.

EFFECT OF DESOXYCORTICOSTERONE ACETATE ON THE BLOOD PRESSURE OF MAN

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In 1939 attention was called to 2 patients whose arterial blood pressure exceeded normal limits in the course of treatment with desoxycorticosterone esters for Addison's disease.[1] Since that time these observations have been confirmed and extended.[2] Studies in animals have also revealed an elevation of blood pressure following the administration of desoxycorti-

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1. Loeb, R. F.; Atchley, D. W.; Ferrebee, J. W., and Ragan, C.: Observations on the Effect of Desoxycorticosterone Esters and Progesterone in Patients with Addison's Disease, Tr. A. Am. Physicians **54:** 285-296, 1939.

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costerone esters.[3] Recently Selye and his co-workers have reported the appearance of vascular lesions in chicks, rats, dogs and other animals following the sustained use of this drug.[4]

In these reports concerning the effect of desoxycorticosterone, it has not been apparent whether the observed increase in blood pressure is due to salt and water retention or to some other unexplained action of the hormone. In order to clarify this problem, it seemed desirable to study the effects of desoxycorticosterone acetate [5] and of sodium chloride on the blood pressure, blood volume and sodium concentration of the blood in comparable groups of patients with Addison's disease. In addition, it seemed of importance to determine the action of desoxycorticosterone acetate and of sodium chloride in a group of patients without adrenal disease and without an underlying disturbance of electrolyte and water metabolism.

I. EFFECT OF SODIUM CHLORIDE AND DESOXYCORTICOSTERONE ACETATE IN ADDISON'S DISEASE

Clinical Material and Methods.—Observations are reported on a series of 15 patients treated with sodium chloride alone and a group of 24 cases treated with desoxycorticosterone acetate with or without additional salt. Included in the second series are 7 patients who, following treatment with sodium chloride alone, were later treated with desoxycorticosterone acetate and are therefore listed in both groups.

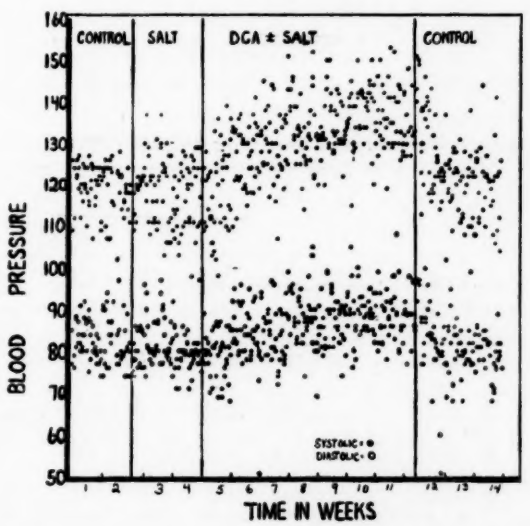
In all cases the diagnosis of hypoadrenalism was established in the wards of the Presbyterian Hospital clinically as well as chemically by a decrease in the sodium concentration of the blood serum during an addisonian crisis or as a result of the withdrawal of salt from the diet. With rare exceptions, all patients were subsequently examined in the outpatient department at intervals of three months or less. The blood pressure was recorded under similar conditions on each visit to the outpatient department by one of a small group of observers. When abnormal values were found, repeated readings were made for confirmation.

Sodium chloride was given in almost all instances in the form of enteric coated tablets, but a few patients, particularly in the earlier years of treatment, took their salt either in capsule form or in drinking water. The parenteral administration of salt was resorted to in the occasional intercurrent crises. The desoxycorticosterone acetate was given subcutaneously in daily injections except to 2 patients, to whom it was administered every other day. Pellets were later implanted subcutaneously in 6 patients, 2 of whom were subsequently returned to the injection form of therapy.

Plasma volumes were determined after twenty minutes of recumbence with the blue dye T. 1824 and calculated from the optical density of a serum sample drawn ten minutes after injection of the dye. The optical density was measured with the photoelectric colorimeter, the results being compared with the estimated normal values based on square meters of body surface area.[6] Total blood volumes were calculated from the plasma volume directly by the hematocrit. Sodium was determined in the blood serum directly [7] or, at times, in the absence of nitrogen retention, indirectly by the summation of the carbon dioxide content expressed as milliequivalents per liter and the chlorine concentration of the serum expressed as milliequivalents per liter plus 10.[8] Cold pressor tests were carried out according to the method described by Hines and Brown.[9]

RESULTS

Treatment with Salt Alone.—In this group of 15 patients (table 1) there were 11 men and 4 women, with a mean age of 37 years (standard deviation 6.7). The average period of treatment with salt alone was more than three years in this series. All the members of this group were maintained in electrolyte balance on daily oral doses of sodium chloride in excess of that in the diet. No significant hypertension developed



Effect of desoxycorticosterone acetate on the blood pressure of 3 patients without adrenal disease.

in any of these patients. At no time did the recorded diastolic pressure exceed 90 mm. of mercury. In only 2 patients were systolic values observed above 140 mm. of mercury and then on only one and two readings respectively over a period in which many lower values were recorded. The plasma and total blood volumes were within accepted normal limits in the 3 patients of this series on whom measurements were made. These determinations were made after many months of sustained salt therapy and when serum sodium concentrations were normal. The cold pressor test was carried out in 6 of this salt treated group at the same time. The results were negative in 3 patients, equivocal in 1 and positive in 2.

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Treatment with Desoxycorticosterone Acetate With or Without Addition of Salt.—In the group of 24 patients with Addison's disease receiving desoxycorticosterone acetate (table 2) there were 17 males and 7 females, having a mean age of 35 years (standard deviation 10.8). All but 5 were followed for more than one year, the average period of observation being two years. In this series repeated blood pressure readings in excess of 140/90 were observed in 12 patients, an additional patient (Ku) having a level of 140/95 at the time of her last visit only. Of these 12 patients, 1 (Deu) had definite antecedent hypertension, another (To) had a history suggestive of angina pectoris before therapy, a third (Wh) came to autopsy, at which time pronounced renal arteriolar sclerosis was found as well as Addison's disease, and a fourth (Ha) was known to have had a labile systolic pressure reaching a maximum of 152 mm. of mercury while a high school student and before the development of hypoadrenalism.

Excluding these 4, there remained 8 patients who gave no history and presented no signs or symptoms to suggest previous or coincidental cardiac, vascular or renal disease. The average age of these patients, in whom repeated blood pressure levels exceeding 140/90 developed in the course of treatment with desoxycorticosterone acetate, was 38 years (standard deviation 6.8). Six of the group were males. The administration of extra sodium chloride was not a constant factor, as 3 received no more salt than that contained in their regular diet. Hypertension developed at different lengths of time after the start of desoxycorticosterone acetate therapy, but the time of its appearance could be measured in weeks or months rather than in days. In 2 instances it appeared within one month, in another not until seven months, and in the remainder the time of onset fell between these intervals. Of particular interest was 1 patient (Fi) whose blood pressure at no time exceeded 118/76 for one year during which his disease was controlled by sodium chloride alone, but

TABLE 1.—*Patients with Addison's Disease Treated with Salt Alone*

Name	Age	Sex	Duration of Treatment	Average Daily Dose of Added Salt, Gm.	Maximum Blood Pressure		Plasma Volume, Cc.	Estimated Plasma Volume, 1,600 Cc. per Sq. M. Surface Area	Hematocrit, per Cent Cells	Comment
					Systolic	Diastolic				
1. Fi	33	♂	1 yr. 1 mo.	12	118	76	.....	.....	..	Subsequently treated with desoxycorticosterone
2. Del	40	♂	1 yr. 3 mos.	15	110	85	.....	.....	..	Subsequently treated with desoxycorticosterone
3. Pol	20	♂	1 yr. 5 mos.	10	110	70	2,660	2,920	45	Subsequently treated with desoxycorticosterone
4. Bu	31	♂	1 yr. 10 mos.	12	120	82	.....	.....	..	Subsequently treated with desoxycorticosterone
5. Ol	34	♂	2 yrs.	18	130	86	.....	.....	..	
6. So	45	♂	2 yrs. 5 mos.	10	122	80	.....	.....	..	
7. Fl	35	♀	2 yrs. 8 mos.	12	106	80	.....	.....	..	
8. Wen	41	♀	2 yrs. 8 mos.	7	138	90	.....	.....	..	Only one blood pressure recorded above 130/80
9. Ga	33	♂	2 yrs. 10 mos.	12	124	80	2,840	2,440	47	Subsequently treated with desoxycorticosterone
10. Be	45	♂	3 yrs. 1 mo.	15	140	85	.....	.....	..	Only one blood pressure recorded above 122/80
11. Ch	34	♀	3 yrs. 6 mos.	8	100	74	.....	.....	..	Subsequently treated with desoxycorticosterone
12. Wil	49	♂	3 yrs. 7 mos.	10	125	80	.....	.....	..	
13. Wes	33	♂	4 yrs. 10 mos.	6	120	80	.....	.....	..	Subsequently treated with desoxycorticosterone
14. Pon	42	♂	7 yrs. 3 mos.	12	145	90	2,490	2,720	44	In over 60 determinations, systolic > 130 twice systolic > 140 mm. once
15. Fr	38	♀	9 yrs. 7 mos.	10	142	90	.. .	.....	..	In over 50 determinations, systolic > 130 three times, systolic > 140 mm. twice

TABLE 2.—*Patients with Addison's Disease Treated with Desoxycorticosterone Acetate, With or Without Added Salt*

Name	Age	Sex	Duration of DCA Treatment	Average Daily Dose		Maximum Blood Pressure		Plasma Volume, Cc.	Estimated Plasma Volume, 1,600 Cc. per Sq. M. Surface Area	Hematocrit, per Cent Cells	Comment
				DCA, Mg.	Salt, Gm.	Systolic	Diastolic				
1. Fi	34	♂	2 mos.	6	0	150	130	.....	.....	..	Repeated blood pressure over 140/90
2. Ch	38	♀	5 mos.	8	2	115	80	.....	.....	..	
3. Gr	23	♀	8 mos.	4	4	120	80	.....	.....	..	
4. Wh	45	♂	8 mos.	3	5	175	110	.....	.....	..	Repeated blood pressure over 140/90; electrocardiogram showed left preponderance before DCA treatment
5. Ru	25	♂	8 mos.	4	0	155	95	2,740	2,960	45	Repeated blood pressure over 140/90
6. Ma	41	♀	10 mos.	3	1	160	98	2,630	2,660	48	Repeated blood pressure over 140/90
7. Sc	22	♂	1 yr. 2 mos.	3	0	120	80	.....	.....	..	
8. To	46	♂	1 yr. 2 mos.	5	0	154	104	.....	.....	..	Repeated blood pressure over 140/90; precordial pain, left preponderance by electrocardiogram before DCA treatment
9. Mc	35	♂	1 yr. 7 mos.	6	2	150	104	.....	.....	..	Repeated blood pressure over 140/90
10. Wes	37	♂	1 yr. 7 mos.	5	2	150	95	.....	.....	..	Repeated blood pressure over 140/90
11. Ku	26	♀	1 yr. 7 mos.	3	0	140	95	.....	.....	..	Diastolic > 90 mm. on last visit only
12. Za	54	♂	1 yr. 8 mos.	5	0	130	80	.....	.....	..	
13. Wo	48	♂	1 yr. 8 mos.	2	3	180	102	3,095	2,800	42	Repeated blood pressure over 140/90
14. Br	46	♀	1 yr. 9 mos.	4	2	160	100	2,740	2,420	46	Repeated blood pressure over 140/90
15. Ha	22	♂	1 yr. 9 mos.	5	0	160	96	.....	.....	..	Repeated blood pressure over 140/90; known to have labile systolic blood pressure before Addison's disease
16. Di	27	♂	2 yrs. 5 mos.	2	5	115	80	.....	.....	..	
17. Wis	11	♀	2 yrs. 5 mos.	3	4	108	85	.....	.....	..	
18. Bu	33	♂	2 yrs. 11 mos.	4	0	122	80	.....	.....	..	
19. Jo	41	♀	3 yrs. 1 mo.	3	0	130	88	.....	.....	..	
20. Del	42	♂	3 yrs. 3 mos.	5	4	140	90	.....	.....	..	
21. Pol	21	♂	3 yrs. 4 mos.	4	3	122	90	.....	.....	..	
22. Ma	27	♂	3 yrs. 8 mos.	6	0	112	80	.....	.....	..	
23. Ga	36	♂	3 yrs. 9 mos.	2	0	158	106	.....	.....	..	Repeated blood pressure over 140/90 during first year of DCA therapy only
24. Deu	50	♂	3 yrs. 9 mos.	4	0	180	110	.....	.....	..	Repeated blood pressure over 140/90; hypertension present before Addison's disease

who then developed hypertension within two months after starting desoxycorticosterone actetate therapy without additional salt.

In only 1 patient (Ga) was the elevated blood pressure transient. The remainder continued to show a hypertension while under treatment, except in instances in which the dose of desoxycorticosterone acetate was reduced either with or without concomitant decrease in serum sodium concentration to abnormally low levels. At no time, however, did the hypertension persist when abnormal cardiovascular signs, in contrast to the rapid cardiac dilatation and failure which may develop when excessive doses of desoxycorticosterone acetate and salt are given in the treatment of an addisonian crisis. In the latter patients hypertension does not appear.

Cold pressor tests were positive in 3 of 6 patients who did not develop hypertension after prolonged treatment with desoxycorticosterone acetate. In 5 of the group who exhibited abnormal increases in blood pressure, the cold pressor test was positive in 3, equivocal

TABLE 3.—*Other Measurements and Laboratory Data on Three Patients with No Adrenal Disease Treated with Desoxycorticosterone Acetate*

Patient	Period	Week	Weight, Lbs.	Venous Pressure, Mm. H_2O	Vital Capacity, Cc.	Circulation Time, Sec.	Cardiothoracic Ratio	Plasma Volume, Cc.	Serum Protein, Gm. per 100 Cc.	Hematocrit, per Cent Cells	Nonprotein Nitrogen, Mg. per 100 Cc.	PSP Excretion in 2 Hrs.	Urine: Specific Gravity	Urine: Albumin	Urine: RBC, per High Power Field	Urine: Casts, per High Power Field
Be	1	1	98-100	50	2,800	..	0.46	2,400	7.0	42	32	50	1.009	+	1	0
		2		..	.....	..	0.46	.....	...	..	..	..	1.014	0	1	0
	2	3	101-103	60	2,600	..	....	2,360	7.5	42	..	..	1.010	+	0	0
		4														
	3	5	102-108	80	2,500	..	....	.....	...	..	..	..	1.026	+	2	0
		6			2,600											
		7	105-107	80, 100,	2,500	20	....	.....	...	..	..	..	1.026	++	0	0
		8		64	2,400											
		9		90	2,200	..	0.49									
		10	106-109	80	2,400	..	0.51	2,520	7.1	41	..	55	1.024	++++	2	0
		11		..	.....	..	0.51									
	4	12		80	2,600											
		13	104-107	70	2,700	..	0.41	2,180	...	..	..	..	1.014	+	2	Rare
		14		..	2,600								1.022	+	6	0
Ch	1	1	134-137	25	3,200	25	0.41	2,620	7.5	49	39	45	1.030	+	0	0
		2		45		23										
	2	3	135-136	35	.....	..	0.40	2,710	7.2	46	..	..	1.034	+	3	0
		4														
	3	5	136-142	75	3,600	..	....	.....	...	..	..	..	1.010	0	2	0
		6			2,500											
		7	139-141	75, 95, 65	2,400	25	0.43	.....	...	..	..	..	1.023	0	0	0
		8														
		9		80	2,800											
		10	138-141	75	2,700	..	0.46	3,530	7.0	44	..	75	1.018	0	0	0
		11		85	2,900	..	0.48									
	4	12			2,800	..	....	.....	...	..	..	..	1.024	0	0	0
		13	136-140	40	.....	..	0.41	3,180								
		14		..	2,600											
Va	1	1	163-164	118*	2,700	11	....	.....	...	..	32	57	1.026	0	3	0
		2														
	2	3	162-164	105	2,600	..	0.56	2,450	7.2	44	..	..	1.026	+	0	0
		4														
	3	5	163-166	85	2,100	..	....	.....	...	..	..	..	1.022	0	0	0
		6			2,300											
		7	160-165	100	2,500	..	....	.....	...	..	..	..	1.020	0	1	0
		8			2,600											
		9		58	2,100	..	0.60									
		10	158-164	105	2,000	..	0.56	2,680	7.0	49	..	53	1.026	+	2	Rare
		11		..	.....	..	0.57									
	4	12		80	2,400	..	0.52	.....	...	..	..	80	1.027	+++	50+	0†
		13	156-159													
		14		..	.....	..	....	3,080								

* Deformities and immobility of elbows and shoulders made accurate measurements impossible.
† Associated with ureteral calculus.

the sodium concentration fell below 133 milliequivalents per liter. On the other hand, elevation of the sodium level above the normal of 141 milliequivalents per liter was not a factor in the development of hypertension. In addition, blood pressure levels bore no relationship to the rare appearance of minimal peripheral edema resulting from the administration of desoxycorticosterone acetate. In 4 patients who developed hypertension on desoxycorticosterone acetate, the plasma and total blood volumes were within accepted normal limits, determinations being made at a time when the blood pressure was significantly elevated and the serum sodium concentration was normal. Repeated examinations of the urine and also of the retinal vessels revealed no abnormalities. The hypertension has not, up to the present time, been accompanied by symptoms or in 1 and negative in 1. All of the cold pressor tests were carried out at a time when the serum sodium concentration was normal.

II. EFFECT OF SALT AND DESOXYCORTICOSTERONE ON PATIENTS WITHOUT ADRENAL DISEASE

The following study was undertaken in order to determine if the effects of desoxycorticosterone acetate on the blood pressure of patients with Addison's disease could be reproduced in individuals without disease of the adrenal glands.

Clinical Material and Methods.—Observations were made on 3 young males without hypertension and without a history of cardiac, renal or adrenal disease. All were patients in the First Medical Service (Research Division) of the Goldwater Memorial Hospital, 2 (Be

and Va) with severe rheumatoid arthritis of the Marie-Stümpell type and 1 (Ch) with mild bronchial asthma. At the start of the experiment 2 showed mild albuminuria without evidence of disturbed renal function.

The study was divided into four periods: (1) a two week control period, (2) a two week period of high salt intake (10 to 20 Gm. daily in the form of enteric coated sodium chloride tablets), (3) seven weeks during which each patient received 10 mg. of desoxycorticosterone acetate daily subcutaneously plus varying amounts of salt (0 to 10 Gm. of enteric coated sodium chloride tablets) and (4) a final period of three weeks immediately following the withdrawal of desoxycorticosterone acetate and extra salt.

During the study these patients were afebrile and the extent of their daily activity about the wards did not vary. They ate the regular ward diet and were weighed at a fixed hour at least every other day. Daily records of fluid intake and output were kept. Throughout the period of observation the blood pressure was recorded twice a day. Each recording was the average of five readings, taken in almost all instances by one of two observers. It was ascertained at the start of the experiment that there was no significant difference in pressure between the two arms.

In addition to these measurements, certain other data were obtained at intervals during the study and are recorded in table 3. Heart size was reported as the cardiothoracic ratio. Plasma volume determinations were made as described but with the optical density measured by the Koenig-Martens visual spectrophotometer.[10] The circulation times were measured with a 20 per cent solution of sodium dehydrocholate (3 cc. intravenously). Only 1 of the 3 (Va) had a positive cold pressor test[9] as determined at the start of the experiment.

RESULTS

Blood pressure readings on all 3 patients during the four periods of the study are shown together in the accompanying chart. In both the control period and the period of salt administration without desoxycorticosterone acetate no significant change in blood pressure levels or body weight was noted. After about two weeks on desoxycorticosterone acetate all 3 patients showed a progressive elevation of blood pressure, 2 gaining a small amount of weight. Only 1 subject (Va) developed symptoms, complaining of severe headaches during the last few weeks on desoxycorticosterone acetate, with the appearance of a subconjunctival hemorrhage and a rise in pressure to 160/108 during the final week. In the final period following the discontinuance of desoxycorticosterone acetate and salt administration, blood pressures returned rapidly to control levels and each of the 3 patients lost a few pounds of weight.

One patient (Va) developed minimal ankle edema during the period of salt administration, and this increased during the first week of salt and desoxycorticosterone acetate therapy, so that sodium chloride tablets were discontinued. This was followed by almost complete resorption of the edema. The second patient (Be) had minimal periorbital and ankle edema during the first week on desoxycorticosterone acetate, but this disappeared completely when the dosage of salt tablets was reduced from 10 to 5 Gm. daily. At the time the edema appeared, neither patient had gained significant weight or showed any accompanying urinary changes or evidence of cardiac decompensation as judged by symptoms, vital capacity and venous pressure measurements. The third patient (Ch) gained 6 pounds (2.7 Kg.) without apparent edema in the first week on desoxycorticosterone acetate, but was able to continue 10 Gm. of added salt a day until the final period without further gain.

No significant changes in the electrocardiogram were observed. In all 3 patients there was a small increase in the cardiothoracic ratio and some reduction in vital capacity. Two of the 3 patients showed slight increases in venous pressure, which, however, did not exceed normal limits. No consistent alteration in plasma volume resulted from desoxycorticosterone acetate therapy. Thus, 1 subject showed no significant change in plasma volume and a second had a rise of 800 cc. at the end of the desoxycorticosterone acetate period. The plasma volume in the third patient increased only 230 cc. during the period of desoxycorticosterone acetate therapy. His plasma volume subsequently rose another 400 cc. three weeks after his blood pressure had returned to the control level following the discontinuation of desoxycorticosterone acetate.

The unexplained albuminuria noted in 1 patient (Be) increased during the last two weeks of desoxycorticosterone acetate therapy but decreased during the final period. The mild albuminuria found at the start of the experiment in a second subject (Ch) cleared completely during the course of the experiment. Just before the end of the last period, after desoxycorticosterone acetate and salt had been withdrawn, 1 subject (Va) developed pain in the left flank and gross hematuria; a left ureteral stone was later demonstrated. During desoxycorticosterone acetate therapy the ability to excrete phenolsulfonphthalein was not reduced in any of these patients.

COMMENT

The development of hypertension in 8[11] of 24 patients with Addison's disease when under treatment with desoxycorticosterone acetate confirms earlier observations suggesting that this hormone may have an effect on the blood pressure. Since this pressor effect of desoxycorticosterone acetate has furthermore been demonstrated in 3 subjects without adrenal disease, it cannot be considered a phenomenon associated solely with hypoadrenalism.

The mechanism of this elevation in blood pressure is not clear, but as yet there is no evidence in the group studied that it leads to progressive arteriolar changes such as may occur in hypertensive vascular disease or have been reported in animals by Selye.[4]

From the present study, the development of hypertension cannot be ascribed to the restoration of the electrolyte and fluid balance to normal in patients with previous adrenal insufficiency. This restoration occurs promptly when acute hypoadrenalism is treated with adequate salt and replacement therapy, whereas the hypertension observed after treatment with desoxycorticosterone acetate requires weeks or months to become apparent. Also no abnormal increase in blood pressure appeared in the group of addisonian patients treated with salt alone over long periods of time, despite the fact that all those patients in whom it was measured

10. Noble, R. P., and Gregersen, M. I., to be published. Dr. Noble gave assistance in these determinations.

11. Four additional patients developing hypertension were excluded because of possible preceding cardiovascular disease.

maintained a normal serum electrolyte pattern and a normal blood volume.

It is apparent that the elevation of blood pressure cannot be correlated with excessive retention of salt or water in the circulating blood or with the development of edema. In the group of addisonian patients treated with desoxycorticosterone acetate the appearance of hypertension was not associated with abnormally high concentrations of the sodium ion in the blood serum. Furthermore, the circulating plasma volume lay within normal limits in 4 desoxycorticosterone acetate treated patients with Addison's disease at a time when their blood pressures were significantly elevated. In addition, the rise in blood pressure following the administration of desoxycorticosterone acetate in the group without adrenal disease was not consistently associated with an abnormal increase in blood volume. There was no correlation between the appearance of hypertension and the excessive accumulation of interstitial fluid in the addisonian patients treated with desoxycorticosterone acetate.

The possibility exists that unrelated hypertension may have been present in all of the group of addisonian patients who developed abnormal elevation of blood pressure during treatment with desoxycorticosterone acetate. This, however, seems improbable because of the fact that none of the patients in the comparable group treated with salt alone developed hypertension, although they were maintained in normal electrolyte and water balance. Furthermore, none of the patients who developed hypertension with desoxycorticosterone acetate therapy had elevation of blood pressure while on earlier treatment with salt alone.

There was no correlation between the appearance of hypertension and a positive cold pressor test in either the addisonian or the control group in the present study. It would therefore appear unlikely that a labile vascular system, as manifested by a positive cold pressor test, is the determinant for the development of hypertension with desoxycorticosterone acetate.

The mechanism of the elevated blood pressure following the prolonged administration of desoxycorticosterone acetate remains obscure. It does not appear to be referable either to abnormalities in the retention of salt and water or to underlying hypertensive disease. It seems probable that desoxycorticosterone acetate acts directly or indirectly on the peripheral vascular system.

CONCLUSIONS

1. The appearance of hypertension in a number of patients with Addison's disease in the course of prolonged treatment with desoxycorticosterone acetate has been confirmed. No similar increase in blood pressure followed the prolonged administration of salt alone.

2. In 3 patients without adrenal disease, a gradual increase in blood pressure has been observed in association with the administration of desoxycorticosterone acetate. The blood pressure in these patients returned to control levels within two weeks following the withdrawal of desoxycorticosterone acetate.

3. The increase in blood pressure cannot be correlated with abnormal retention of the sodium ion or with an increase in circulating blood volume.

4. The increase in blood pressure observed is not apparently dependent on an abnormally labile peripheral vascular system as measured by the cold pressor test.

620 West 168th Street.

Clinical Notes, Suggestions and New Instruments

SPONTANEOUS RUPTURE OF AORTA IN SYPHILITIC AORTITIS WITH ANEURYSM

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That spontaneous rupture of the aorta in syphilitic aortitis without aneurysm is a rare event is indicated by the fact that it was encountered only twice in 73,607 necropsies performed in the thirteen general hospitals of the twenty-two hospitals of the Department of Hospitals of the city of New York. The literature on the subject seems to be limited to the statement that "a syphilitic aorta never ruptures unless it has given rise to aneurysm." [1] The 2 cases referred to are recorded in this report.

REPORT OF CASES

CASE 1.—*History.*—A man aged 40, Italian, a rubbish collector, was admitted to Bellevue Hospital in a moribund state and died twenty-five minutes later. It was said that he had been well until two hours before admission, when he complained of faintness, substernal pain and shortness of breath. On admission he was cyanosed, the hands were cold, no radial pulses could be felt, breathing was labored and the veins of the neck were engorged. The heart sounds were weak and distant. While in the hospital the patient vomited on frequent occasions. The condition of the patient's blood pressure before he entered the hospital was not learned.

Necropsy.—The body was well developed and well nourished, 162 cm. in height and weighed about 77 Kg. There was no external edema. The precordial area was greatly enlarged, the lungs pushed aside by the bulging pericardial sac. When the pericardium was opened, dark red fluid blood escaped. In the dependent part of the sac there was a large dark red jelly-like clot. The heart was contracted, and very little blood was found in it. The wall of the left ventricle was moderately thickened. The endocardium was well preserved with the exception of the posterior and right anterior aortic cusps, which were thickened at the margins adjoining the commissures. The commissures were widely separated. Lying beneath and elevating them were several hyaline plaques, which encircled the aorta immediately above the valves. Some of these plaques were finely wrinkled. Just above the posterior aortic cusp there was an irregularly lacerated aperture measuring 6 mm. in length and 4 mm. in breadth. The edges were serrated, reddish and infiltrated with blood. The remainder of the aorta appeared to be well preserved. The orifice of the right coronary artery was stenosed; that of the left was apparently normal.

Microscopic Examination.—Aorta: The adventitia was greatly thickened, owing to the presence of patches of connective tissue which were more or less well supplied with poorly nucleated fibroblasts and areas in which collagenous fibers were hyalinized. Scattered through the adventitia were large collections of lymphocytes and in other places smaller collections composed almost exclusively of plasma cells. The vasa vasorum were thickened and the lumens compressed. Some of them were surrounded by mantles of lymphocytes and plasma cells. Their walls were made up of loosely arranged fibromuscular tissue. In the media of the aorta the muscle was almost completely replaced by fibrous tissue. Those fibers that remained were granular and almost completely bereft of nuclei. The elastic tissue was relatively plentiful and the individual fibers were thickened, some of them split or frayed at the ends, others fragmented. Scattered through the media were numbers of small hyalinized scars arranged aound the lumens of small vessels. Near the point of perforation the media showed a large hyalinized scar in which practically no nuclei were visible.

From the Laboratories of Pathology, Bellevue and Goldwater Memorial Hospitals.

1. Criteria Committee: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, New York Heart Association, 1939, pp. 35 and 226.

The intima in places was elevated and made up of a few fibroblasts lying close to the media. The connective tissue in the intima was anuclear, hyalinized and, in places, granular and necrotic.

Microscopic examination of the remaining organs, including the kidneys, showed nothing of importance in the present connection.

CASE 2.—*History.*—A man aged 79, Italian, who died within a period of about five minutes while bathing his face, had been under observation for five weeks because of signs of nephrosclerosis and so-called hypertensive heart disease. While in the hospital the blood pressure varied from 143/100 to 210/140. The Wassermann reaction was negative.

Necropsy.—The precordial area was enormous and was bluish red. The pericardium was distended by clotted blood in which the contracted heart was completely buried. The heart, with the attached aorta, weighed 760 Gm. The left ventricle measured 2.5 cm. in thickness just below the level of the posterior mitral cusp. When the heart was opened the endocardium was found to be smooth and glistening. The ascending aorta was dilated toward the right, where it was thinned. The aortic cusps were thin and pliable. The inner surface of the aorta from commencement to bifurcation, but particularly in the ascending portion, was light grayish and showed numerous firm elevated pearly plaques, some of which were wrinkled. On the left side of the aorta about 5 cm. above the sinuses of Valsalva was an oblique linear perforation. It measured 4 cm. in length and its edges were irregular and freshly hemorrhagic. The immediately surrounding adventitia was infiltrated with blood.

The kidneys were about normal in size. The capsules stripped without difficulty, leaving an irregularly scarred surface. Between the areas of scarring the surface was finely granular. On section the cortices were narrow and retracted, especially at the extreme periphery.

Microscopic Examination.—Aorta: The adventitia was moderately thickened and, in places, sclerotic and hyalinized. Scattered through it were collections of lymphocytes with a fairly liberal admixture of plasma cells. In some instances the vasa vasorum showed only slight thickening of the fibromuscular walls, occasionally accompanied by reduplication of the lining endothelium. In other instances the vasa vasorum were decidedly thickened, owing to hyperplasia of the muscular coat and reduplication of the endothelial lining, producing either eccentric or concentric and almost complete occlusion of the lumens. A few of the vasa vasorum were surrounded by collections of lymphocytes and a sprinkling of plasma cells. The media of the aorta was thinned and partly replaced by hyalinzed connective tissue, which in places was distributed in such fashion that intima and adventitia were separated by a thin layer of compressed and atrophied muscle and remnants of elastic tissue. In addition, the media was replaced at intervals by scar tissue distributed around small blood vessels with thin walls. In specially stained sections the elastic tissue seemed to be greatly reduced in quantity and the individual fibers were sometimes thinned, at other times thickened. In numerous instances they had lost their wavy contours. Some of them were fragmented; others were reduced to shreds or clumps of granular débris. The intima was thrown into moundlike formations composed of poorly cellular, frequently sclerotic and sometimes hyalinized connective tissue.

Liver: In the liver were numerous focal collections of lymphocytes, many of which were associated with an admixture of a few fibroblasts and plasma cells. Some of these focal collections, which lay among and displaced the parenchyma cells, were centrally necrotic (miliary gummas).

Kidneys: The kidneys were congested, especially in the cortex, where the vessels in places were distended. Immediately beneath the capsule were numerous wedge-shaped areas composed of connective tissue supporting a few tubules in different stages of compression and dilatation, injected capillary vessels, glomeruli in various stages of fibrosis, some of them completely hyalinized, and lymphocytes arranged diffusely or densely in patches. Deeper in the cortex many of the arterioles were sclerotic and sometimes hyalinized. The arteries were similarly changed. The glomeruli were congested. In some of them the capsular space contained coagulated granular material. In other instances the glomeruli showed productive capsular changes passing through various gradations to complete sclerosis and hyalinization. The convoluted tubules were moderately dilated, their lining epithelium granular and their lumens containing débris.

COMMENT

When syphilitic aortitis first attracted attention in this country it was observed that the microscopic changes were usually characterized by signs of activity.[2] As a rule there was nothing vague or indeterminate in the histologic picture. Gradually a period of transition set in and the tissues began to show modifications in the direction of inactivity. For some years past it has not been common in my experience to encounter syphilitic aortitis of other than the inactive or "burned out" variety. Inactivity appears to be brought about irrespective of treatment because inquiry almost invariably reveals that treatment was either neglected or inadequate.

In syphilitic aortitis the process of vascularization extends from the adventitia well into the media, replacing both muscle and elastic fibers, ending in the formation of scars. The intimal reaction, which consists of overgrowth of the subendothelial fibroblasts progressing to connective tissue formation followed by hyalinization, is commonly interpreted as a compensatory process. However this may be, the fact remains that the vessel wall is comparatively well fortified, although frequently injured in such fashion as to permit true aneurysmal dilatation and spontaneous rupture. In the 2 cases here recorded the changes in the aortic wall seem to me to have attained a degree of severity beyond that of the customary destruction and replacement of tissue, notably in the media. In the first case the elastic fibers, although plentiful, were thickened and shortened and had lost their wavy outlines, indicating, no doubt, loss of elasticity, and the muscle substance was almost completely replaced by fibrous tissue. In the other case the elastic fibers were reduced in numbers and thinned, and the intermuscular connective tissues were sclerotic and hyalinized, sometimes to an extreme degree. In other words, the histologic changes in both cases showed injury of the vessel wall to an extent which seems to justify the appellation of a "burned out" process. It is true that most "burned out" syphilitic aortas do not rupture spontaneously, and doubtless some additional factor or factors are operative in those circumstances in which spontaneous rupture occurs without aneurysm. In case 1 of this report there was no obtainable record of the condition of the patient's blood pressure previous to admission to the hospital. Nevertheless, because of thickening of two of the aortic cusps and wide separation of the commissures it may be safely assumed that the patient suffered from some degree of aortic regurgitation attended with elevation of systolic blood pressure. In the second case there seems to be no doubt that rupture of the aorta was due to sudden increase in a degree of blood pressure already considerably above that of the normal.

In those cases of medial necrosis of the aorta in which spontaneous incomplete rupture occurs with the production of so-called dissecting aneurysms, the patients' blood pressure is practically always high and is commonly believed to be the immediate cause of the tear in a weakened vessel wall. It seems reasonable to anticipate that an elevation of blood pressure will be eventually shown to operate in spontaneous rupture of the aorta in uncomplicated syphilitic aortitis. In that section of his book on Human Pathology dealing with the subject of "dissecting aneurysm," Karsner[3] states that "the lesion is rare in syphilitic aortitis." From this it may be inferred that "dissecting aneurysm" sometimes follows incomplete rupture of the scarred media of the syphilitic aorta and that an elevation of blood pressure is the immediate cause, as it is in "dissecting aneurysm" associated with medial necrosis of the aorta. Even from the scanty information available, the opinion seems to be justified that the rarity of spontaneous rupture of the aorta in syphilitic aortitis without aneurysm is due to the fact that in pure, uncomplicated syphilitic aortitis the blood pressure is normal or approximately so.

2. Symmers, D., and Wallace, G. H.: The Etiology of Syphilitic Aortitis, J. A. M. A. **66**: 397 (Feb. 5) 1916.
3. Karsner, H. T.: Human Pathology, ed. 6, Philadelphia, J. B. Lippincott Company, 1942, p. 392.

Rottino and Poppiti [4] have recently shown that thickening, hyalinization and wrinkling of the intima of the aorta closely resembling the intimal changes in syphilitic aortitis sometimes occur in association with medial necrosis and may be followed by spontaneous rupture and the formation of a "dissecting aneurysm." The naked eye appearances of such an aorta are apt to be deceptive, and microscopic examination should be made to exclude syphilitic aortitis.

CONCLUSIONS

Spontaneous rupture of the aorta in syphilitic aortitis without aneurysm occurs but is extremely rare. Rupture is complete, occurs without "dissection" and is rapidly followed by death from hemorrhage into the pericardial sac. An elevation of blood pressure is probably the precipitating factor in the production of the tear in a vessel wall which has already been severely damaged by syphilis.

THE RAPID IDENTIFICATION OF MUCOID HEMOLYTIC STREPTOCOCCI OF POSSIBLE EPIDEMIC ORIGIN

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In the search for epidemic strains of hemolytic streptococci, earlier investigations were related to the isolation of mucoid strains of hemolytic streptococci. It was pointed out that mucoid encapsulated streptococci have epidemiologic significance.[1] Milk borne epidemics of sore throat and scarlet fever have yielded consistently mucoid forms of beta hemolytic streptococci (Streptococcus epidemicus) if proper mediums and differential methods have been employed.[2]

To identify these mucoid strains readily a culture medium of ascites fluid added to fresh infusion blood agar has been described.[3] As ascites fluid is not always available, the present study was directed to find a simple medium that could be used routinely for the rapid isolation of mucoid strains for grouping and typing.

Various mediums used in army laboratories were tried. Dehydrated brain heart infusion as prepared by Difco with 1.75 per cent agar furnished a satisfactory base for blood agar. Fresh moist plates with 5 per cent human blood inoculated with throat swabs, exudates and slant cultures from various sources gave striking results on both streaked and poured plates. In twelve to twenty-four hours the colonies appear large, mucoid, often ameboid and confluent, then rapidly flatten to smooth or wrinkled phases. Infusion agar prepared with various peptones including neopeptone failed to bring out the large mucoid growth.

In the spring and fall of 1943 in routine cultures of throat and nasopharynx of 150 individuals, including both normal persons and patients with upper respiratory infections, no mucoid hemolytic streptococci were encountered. A few green mucoid colonies proved to be type III pneumococci, none of the green variant of the alpha hemolytic streptococci prevalent during and immediately after the pandemic influenza of 1917-1918.[1] Throat cultures of patients with sore throat, scarlet fever and rheumatic fever, none of which were related to milk borne infection, frequently yielded predominant numbers of mucoid hemolytic streptococci often in pure culture. As previously observed, these streptococci appear etiologically related and can be readily followed and correlated with clinical course, complications and sequelae, especially with reference to rheumatic manifestations.[2]

By Lancefield's method of grouping, the mucoid beta hemolytic streptococci uniformly fell into group A. Typing by Griffith's slide agglutination method classified some strains as type 1, 3 and 14. Many of the mucoid strains were difficult to type clearly by this method and were sent to Dr. M. T. Hamburger, who by the new Wilson-Lancefield capillary precipitin method [4] typed these strains predominantly as 17 and a few 19 and 30.

Type 17 was largely from scarlet fever patients, types 1, 3 and 14 from throats in early stages of rheumatic fever. Types 1 and 14 produced definite purulent arthritis in young rabbits injected intravenously with 0.1 cc. of twenty-four hour broth cultures.

Of special interest are the recent reports of milk borne outbreaks of sore throat and scarlet fever, now traced to serologically specific types of hemolytic streptococci.[5] Among these epidemics type 3 accounted for three outbreaks, 2 and 17 for other episodes. These types appear to be sources of epidemic strains, but no mention is made of any mucoid property. However, our past experience with strains from milk borne epidemics of sore throat has emphasized this important characteristic.[6] The mucoid strains are particularly responsible for the bovine mastitis which is the source of epidemic milk borne septic sore throat and scarlet fever. Experimentally the mucoid strains ascend into the udder by simply smearing the teat and cause a similar mastitis.[7] This aggressive property of the mucoid strains is further demonstrated by the frequency of their occurrence in otitis media, mastoiditis and meningitis complicating sore throat.[8]

SUMMARY

During periods of high incidence of scarlet fever, sore throat and rheumatic fever many beta hemolytic streptococci may be found in throat cultures. Attention to mucoid forms will simplify the isolation of etiologically related strains.

By the use of brain-heart infusion blood agar, mucoid beta hemolytic streptococci can be isolated readily and then grouped and typed to ascertain their epidemiologic importance.

PALINDROMIC RHEUMATISM

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In June 1940 Hench and Rosenberg [1] described a new syndrome called palindromic rheumatism. At that time they described findings in 34 cases. There is much to indicate that this is actually a disease entity. In the army, where one sees so much real and neurogenic arthritis, it is not unusual that an occasional case of palindromic rheumatism should be found. This case is being reported because the condition has only recently been recognized as a disease entity, and it is felt that more cases will be found if the attention of physicians is directed toward this disease.

REPORT OF CASE

History.—A soldier aged 23 from Ohio was admitted to the Station Hospital, Camp Gruber, Oklahoma, with the chief complaint of recurrent attacks of pain and swelling of the wrists and ankles. The soldier had been in the army for one year but was unable to do his required duties because of attacks of joint pain. The attacks were characterized by sudden onset with considerable pain, moderate swelling, mild redness, slight increase in warmth and pronounced disability of

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4. Rottino, A., and Poppiti, R.: Intimal Changes in Medial Degeneration of the Aorta, Arch. Path. **36**: 201 (Aug.) 1943.

From the Sixth Service Command Laboratory, Fort Sheridan, Illinois, and from the Department of Pathology and Bacteriology, University of Illinois College of Medicine, Chicago.

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2. Pilot, I., and Davis, D. J.: Sporadic Septic Sore Throat, J. A. M. A. **97**: 1691 (Dec. 5) 1931.
3. Pilot, I.; Hallman, B., and Davis, D. J.: A Culture Medium for the Isolation of Streptococcus Epidemicus of Septic Sore Throat, J. A. M. A. **95**: 264 (July 26) 1930.
4. Swift, H. J.; Wilson, A. T., and Lancefield, R.: Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. **78**: 127, 1943.
5. Dublin, T. D.; Rogers, E. F. H.; Perkins, J. E., and Graves, F. W.: Milk Borne Outbreaks Due to Serologically Typed Hemolytic Streptococci, Am. J. Pub. Health **33**: 157, 1943.
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7. Davis, D. J.: Bovine Mastitis in Relation to Milk Borne Epidemics, J. Infect. Dis. **60**: 374, 1937.
8. Pilot, I.; Lampert, M., and Davis, D. J.: Otitis Media and Mastoiditis Due to Streptococcus Epidemicus, J. Infect. Dis. **48**: 498, 1931. Pilot and Davis.[2]
1. Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism: A "New," Oft Recurring Disease of Joints (Arthritis, Periarthritis, Para-Arthritis) Apparently Producing No Articular Residues; Report of 34 Cases (Its Relationship to "Angioneural Arthrosis," "Allergic Rheumatism" and Rheumatoid Arthritis), Proc. Staff Meet., Mayo Clin. **16**: 808-815 (Dec. 17) 1941.

the involved joints. No chills, fever or other symptoms were experienced. An attack often began and reached its height in a period of ten to twenty minutes, but most attacks came on over a period of eight to eleven hours. The first attack occurred at the age of 16 years, and subsequent attacks have occurred approximately once or twice a week. Well over two hundred attacks have been experienced. Practically all joints in the body have been involved, but the attacks have been localized largely to the wrists and ankles. Usually only one joint was involved. Some attacks have lasted only thirty minutes, while others caused distress for as long as two weeks. Attacks have been so severe that they cause him to cry out with pain. No known precipitating causes could be elicited. Attacks were not precipitated by nervousness, worry or changes in weather. He was tested for allergic factors, but none were present. The patient's history and his family's history were entirely negative for rheumatic or allergic manifestations. His father died of tuberculosis, but the patient has been frequently checked by roentgenographic and other methods, and at no time has he been found to have this disease. The family history was entirely noncontributory. Some relief was obtained from heat and slight relief from alternately immersing the involved joint in hot and cold water. Acetylsalicylic acid gave temporary relief. Injections of epinephrine did not alter the pain or swelling. The review of systems revealed that he had only light perception in the left eye, because of an old external strabismus. The right eye was essentially normal. He had occasional left frontal headaches, but they were not severe. The cardiovascular, respiratory, gastrointestinal and genitourinary systems were entirely normal. The patient was quite nervous. He had moderate tendency to worry, was quite irritable and was bothered by insomnia to a mild degree. He felt definitely that his condition was gradually getting worse.

Physical Examination.—The patient appeared essentially normal. He was 68 inches (173 cm.) in height and weighed 132 pounds (60 Kg.). The heart was normal in size, rate and rhythm. The blood pressure was 120/80. The lungs were clear. The liver and spleen were not palpable, and no abdominal masses were present. Approximately seven attacks were experienced while he was in the hospital. One attack was observed to appear and reach its height within a period of ten minutes. The duration of this attack was approximately six hours. The right wrist was noted to become slightly swollen, moderately warm and exquisitely tender during each attack. On one occasion there was periarticular swelling of the lateral flexor surface of the right wrist involving an area of approximately 2.5 cm. in diameter. This area was tender and painful. There was no itching, and it did not appear to be due to angioneurotic edema. Both passive and active movement of an involved joint caused much pain. There was no atrophy of the tissues about the involved joints, and roentgenograms of the wrists and ankles were entirely negative. No skin rashes were present, nor was there any evidence of allergic manifestations noted at any time. No fever or chills were present. Laboratory examinations were all within normal limits. The urine showed a specific gravity of 1.023. No albumin was present, and microscopic examinations were negative. The leukocyte count was 8,200, with 68 per cent polymorphonuclears and 32 lymphocytes. The erythrocyte count was 4,000,000, with 81 per cent hemoglobin. Repeated sedimentation rates were normal, as was the electrocardiogram. Agglutination tests for brucellosis were negative. Uric acid was 2.6 mg., cholesterol 115.2 mg. and calcium 9.9 mg. per hundred cubic centimeters. Unfortunately a determination of fatty acids and total lipoids could not be obtained. Skin and food tests for allergy were negative. No relief was noted from injections of epinephrine.

COMMENT

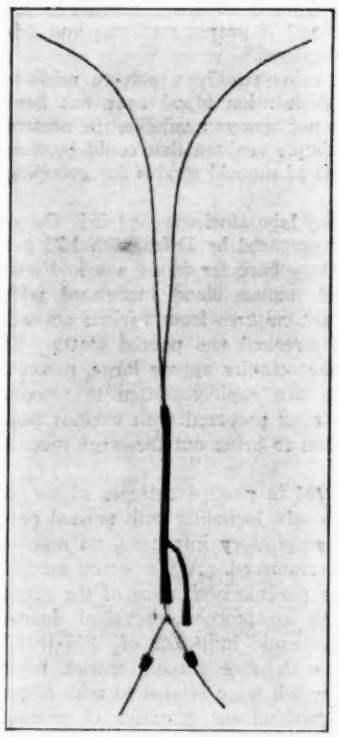
This case represents a typical picture of palindromic rheumatism as described by Hench and Rosenberg.[1] The characteristic features were multiple afebrile attacks of acute arthritis and periarthritis. There were mild redness, moderate to mild swelling, moderate tenderness and pronounced disability of the joint during an attack. Attacks involved only one joint at a time, and they occurred suddenly and were frequently of short duration, lasting from several hours to fourteen days. No constitutional reaction was present, and the sedimentation rate and other laboratory findings were normal. The blood cholesterol was slightly lower than normal, being 115.2 mg. per hundred cubic centimeters, but the exact significance of this is not known. Dr. Hench found the fatty acids and total lipoids moderately elevated in his cases, but unfortunately these tests were not performed in this case. Roentgenograms during and between attacks were normal. No evidence of vasomotor instability was noted. A thorough survey revealed no allergic factors.

This represents a typical case of palindromic rheumatism. Perhaps this syndrome occurs more frequently than is generally realized, and as physicians become cognizant of its features it will be diagnosed more often.

CATHETER INCONTINENCE FOLLOWING CYSTOSCOPY

NORVELL BELT, M.D., WASHINGTON, D. C.

Cystoscopy, with indwelling ureteral catheters as its objective, entails some discomfort to the patient when drainage must be established for a period of time. One of the most annoying sequelae is in the female patient, in whom large quantities of urine pass around the catheters through the urethra. The dilemma of continuous confinement on the bed pan or perpetual changing of bedclothes is a serious nursing problem, to say nothing of the dangers to the patient. The possibility of upper respiratory infections is increased by moisture. There is no rest for the wet.



Apparatus for keeping patient dry after cystoscopy.

The apparatus described here has solved the problem of keeping the patient dry. It consists in threading a Foley female number 22 French catheter, 5 cc. bag capacity, over the distal ends of the ureteral catheters. A copious supply of surgical lubricant is applied to all catheters. The bag is distended after introduction into the bladder, and the bladder outlet is occluded with gentle traction. To facilitate its passage over the ureteral catheters, that portion of the catheter tip including the fenestra is cut off. The protruding ends of the ureteral catheters are threaded in a glass inverted Y tube and brought out on the proper side through cystoscopic nipples and connected with sterile containers. The urine that enters the bladder from around the ureteral catheters may cause some retention. The Y tube may be disconnected and the bladder drained ad libitum. Usually once a day suffices.

Sulfonamide therapy is contraindicated, owing to the danger of the accumulation of crystals around the foreign body. In a few cases in which these drugs were used, removal of the catheter was difficult because of chemical deposits.

Anatomic differences make this apparatus more practical for the female than the male, although it may be used for either sex. Man is not an amphibious animal, and the comfort, rest and dryness results in a grateful patient and solves a nursing problem.

1926 Eye Street N.W.

Special Article

AMERICAN HEALTH RESORTS

TREATMENT OF CONDITIONS AFFECTING THE GENERAL NERVOUS SYSTEM

THE PLACE OF HEALTH RESORT THERAPY

GEORGE B. FLETCHER, M.D.
HOT SPRINGS NATIONAL PARK, ARK.

These special articles on spa therapy and American health resorts were prepared under the direction of the Committee on American Health Resorts. The opinions expressed are those of the authors and do not necessarily reflect the opinion of the committee. These articles may be published later as a Handbook on Health Resorts.

The term health resort may be applied loosely to any place from a "dude ranch" to a well set up spa where facilities are available for therapeutic baths and physical therapy as well as understanding, intelligent medical care and recreational features.

In one category we think of the three R's Rest, Recreation and Recuperation, and in another we think of means of bringing about relief of pain, improvement in muscle tone and coordination whereby a patient may regain, at least in part, that which has been lost.

While climate may be a factor, the most important requirements to be considered are (1) good medical care, (2) adequate facilities, well regulated, for giving the different forms of treatment and (3) a setting which will be conducive to peace of mind in the patient.

There is no place in the setups of spas for the advertising of "miracles," and only facts, unglamorized, should be stated; otherwise there will be the danger of a "racket" developing.

While health resorts do not all have hydrotherapy available, and some resorts, such as those catering to chest diseases, do not need hydrotherapy, the type of patient discussed in this paper will need this service.

An outstanding factor in favor of going to a resort for the "cure" is that a person gets away from worries present at home, meets new people, and, whereas ordinarily he would find too many things to interfere with going to see his doctor, he has nothing else to do but make a business of getting well. He is able to follow a regular schedule without thinking of the office and, seeing others following such a schedule, he does not feel at all out of place. He will follow out his physician's orders, feeling that he is preparing himself to resume his labors in a better physical and mental condition.

Many things may be done with water. We may confine our treatments to underwater or pool baths if these are indicated or, on the other hand, we may go into the other departments where we may receive the tub bath, packs to various parts of the body, sitz baths, salt glows, scotch douches where desired, needle showers, whirlpools, cabinets or massage, and many of these may be combined to bring about results depending on the patient's complaints. For instance, a patient with a lame shoulder may need a douche and hot packs on the shoulder, and one with hemorrhoids or a prostatitis may obtain much comfort from a prolonged sitz bath. It is not unusual for a pool patient, perhaps a "polio" or spastic, to request that he be allowed to take an occasional routine bath as a sort of vacation from the pool.

Lowman,[1] in speaking of pool therapy, states that "it is generally conceded that the medical profession's failure to recognize its value has not only retarded hydrotherapeutic development and use in this country but has caused the adoption of various hydrotherapeutic procedures by unethical cults and quacks." Water, probably the oldest medium of physical treatment, possesses greater possibilities for good in physical rehabilitation than any other modality. Right here it might be said that the United States government, realizing the truthfulness of this statement, is sending here, and probably to other spas, great numbers of soldiers who have developed disabilities from army and navy service. For many years it has been realized that it is easier to perform exercises in the water than under normal atmospheric pressure. This is especially striking in the case of treatment of extremities which have been greatly weakened by paralytic or paretic conditions, so this knowledge has led to the application of underwater treatment to the reeducation of disabled or impaired muscles. Archimedes' law of displacement explains the advantages to be expected by underwater treatments.

The history of the use of water in the treatment of disease, while most interesting, would constitute a complete discussion in itself. Here we are dealing not only with organic disease of the central nervous system but also with the psychoneurotic and other similar mental conditions. The patient who is "just nervous" is depressed, has a feeling of inward tension and is generally unhappy.

A simple classification of the diseases of the central nervous system seen at resorts is as follows:

1. Spastic paralysis.
2. Flaccid paralysis with atrophy.
3. Sensory changes which may accompany either of the foregoing.
4. Peripheral nerve conditions such as neuritis and neuralgia.

Of the functional diseases seen at resorts the following are the most usual:

1. Psychoneurosis.
2. Simple depressions.
3. Involutional depressions which will not be helped by resort treatment alone.
4. Exhaustion states following unusual stress in business or home life or following a prolonged illness.

Then there will be a certain number of patients with Parkinson's disease or the syndrome following encephalitis, together with a few patients exhibiting a fine tremor such as that found in hyperthyroidism.

It is a well known fact that a body in water will weigh much less than it would outside the water; for instance, a body weighing 132 pounds outside the water will weigh only 6 pounds when submerged, and by using this principle it is easy to see why weakened muscles and joints can perform acts which would be impossible without this buoyancy. The psychologic reaction in a patient who has been bedridden is often dramatic when he finds himself able to move in the water whereas in bed he was "just too heavy." The word "pool" has been associated with swimming so long that one may think only in these terms, and we do know that there is a place for supervised swimming along with the other exercises; but unsupervised swimming might cause harm, owing to the fact that the patient may have to learn to swim over again and in doing so find that the old muscles he formerly used are no longer func-

1. Lowman, C. L.: Technique of Underwater Gymnastics, Los Angeles, American Publications, Inc., 1937.

tioning well and there may be a tendency to swim the wrong way just to make progress through the water. That is why swimming should be supervised and the patient be made to swim correctly even though it may be the hard way.

It does not matter so much whether there is a large pool with varying depths of water or a smaller tub arrangement such as the Hubbard tub and its modifications, so long as we have carefully worked out the muscle groups, impaired joints and limitations of motion in order that we may write an intelligent and easily followed set of instructions for the physical therapist who will supervise the treatments.

Poliomyelitis has been in the public mind for years, and the idea prevailed that this disease alone was benefited by underwater therapy; but we have learned that the bulk of our patients will come from those having peripheral nerve injuries, either from disease or from trauma, patients showing poor coordination, those having spasticity, and arthritic patients with contractures and limited motion in joints. By reeducation we bring to the consciousness of the patient what should normally be expected of a group of muscles, and he in turn learns why he cannot perform acts normally and by reasoning begins to try to bring the right muscle or group of muscles into play in a normal manner. This is, of course, where we depend on a well trained physical therapist to see that the patient understands what muscles are defective and how to benefit from the exercises intended to bring about renewed function. One will see a knee joint which cannot be straightened, perhaps because of the patient's having slept with a pillow beneath the knee when the disease was in the acute and painful stage. Then there might be the same condition in an elbow or other joint. Frequently traction may gradually straighten such a joint; but it must be remembered that applying traction on the ordinary bed is not very pleasant to the patient because the body, on account of its weight, literally "hugs" the bed. However, when such traction is applied under water on a special table, the body floats free of the table and the patient, being much more comfortable, will allow more traction to be applied.

Children always like to play in water, which is one reason why they take to the pool as a plaything rather than a treatment; however, the physical therapist should know how much play to allow and how much serious thought should be given to the problem at hand. The little fellows, as in swimming by adults, might easily adopt wrong postures and wrong use of muscles if allowed to move about the easiest way.

Stress has been made on the fact that a physical therapist should be in attendance at all times. At Hot Springs National Park the Department of the Interior will not allow any one to take pool treatments without having been examined by a registered physician and under the care, in the pool, of a graduate physical therapist. Masseurs available in other departments for routine massage are not used in pool treatments except under supervision of the physical therapist.

It is required that the physical therapist make a complete chart of diseased muscles and joints when he first sees the patient after the doctor has made his examination and written his directions; then at frequent intervals he reexamines the defective parts and makes a written report to the patient's physician, thereby keeping him informed of the patient's progress and enabling the doctor, if he so desires, to advise the patient's home physician when the time comes for the patient to go home. When these reports are received it is not infrequent for some changes to be found desirable.

One with a mechanical mind may devise any number of contrivances in a pool to take care of defective function. Bicycles, walking apparatus, floating objects, whirlpools, traction tables and any number of other devices come to mind when one begins to think of what one wishes to accomplish for the individual.

The water temperature of about 90 F. is much less than would be used in the other departments, and some doctors advocate pools of different temperatures for different types of involvement; but it should never be hot enough to bring about exhaustion from the exercises. The expense of heating and cooling water is no small item, but where natural hot water is available this expense is not a factor.

In the other types of baths one must have trained attendants who can follow written directions. Suppose I give a cross section of what may be obtained in this type of bath. The patient is first placed in a large tub with temperature ranging from 90 to 105 F. He may drink two or more cups of hot water and have a brisk rubdown with a bath mitt. If indicated he may go to a "head in" or "head out" cabinet for a few minutes, and this may be followed by a salt glow and scotch douche, or he may go to the sitz bath for five or more minutes at a temperature up to 105 F. Then he may go to the pack room, where hot wet towels are applied to the affected parts, and here he may drink more hot water. If perspiring freely he may wish a cool towel to the head. The next step is the needle shower and a good rubdown with a large rough towel, after which he goes from room to room, each being slightly cooler than the preceding one, until he has reached a temperature corresponding with that on the outside.

There are variations to the foregoing procedures too numerous to mention. Many patients will wish to go to the massage room after the bath or, in case of women, to the beauty parlor. A gymnasium is available at all bath houses, and many persons may like to have a workout before going to the bath. The use of electrical apparatus is not allowed except in the pool, where muscles are tested for reaction of degeneration.

It can readily be seen that times and temperatures are important and must be considered when writing a bathing direction. For instance, a person with low blood pressure would not tolerate high temperatures and prolonged heat as well as one with a normal blood pressure. Then profuse sweating as induced by drinking water and going into cabinets would not be advisable in all cases. It is certainly advisable for every person to be examined before taking baths, but it has not been made obligatory.

Many patients with incurable diseases will go to a health resort year after year because they have derived some benefits and feel that the yearly visits are worth while. They have been made happier by doing so.

It is highly important that the home physician try to cooperate with the resort physician because, after all, the home physician has probably known the patient for many years and can make helpful suggestions which will be welcomed by the resort physician. Some physicians will tell their patients that they can do just as well in their own bathroom as they can elsewhere, but they lose sight of the fact that a supervised hydrotherapeutic program accomplishes something which cannot be accomplished by bathing in the home. Fortunately many physicians welcome the availability of spas for the treatment of some of their difficult patients, and I

have found it advisable and helpful to communicate with the home physician from time to time receiving and applying their suggestions. We of the spas always welcome a letter from the home physician when the patient arrives in our offices.

While baths "per se" may not be the whole story so far as "nervous" patients are concerned, these persons enjoy routine and "something to do" as a vacation from sedatives and other drugs, and the meeting of new people together with the new interests to which they have not been accustomed will enable patients to get away from that state where they may literally draw a circle about their feet and be unable to step out of it. The fact that year after year patients with organic and functional disease of the nervous system have returned to resorts is indication enough that benefits have been obtained by these visits, and this fact alone establishes the importance of resorts in the scheme of life and medical management of disease.

Council on Foods and Nutrition

THE COUNCIL ON FOODS AND NUTRITION HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT.

GEORGE K. ANDERSON, M.D., Secretary.

THE MECHANICAL COW

The "mechanical cow" is a machine manufactured by the United Dairy Equipment Company of West Chester, Pa. The purpose of the machine is to mix water, spray-dried skimmed milk and butter to produce a product which can substitute for milk or cream according to the proportion of ingredients employed. The preparation of an ice cream mixture is also included among the purposes of the machine.

The machine contains a mixing-pasteurizing tank for starting the process; the final product passes over a cooler. The unique feature of the machine consists of a vertical cylinder nearly 2 inches in diameter rotating at high speed (22,000 revolutions per minute), which emulsifies, homogenizes and clarifies the product. The mixed, pasteurized product is drawn into the rotating cylinder from below by centrifugal force. Immediately above the intake a set of vertical blades, moving at the same speed as the cylinder, splashes the product against the cylinder wall with great force, partially emulsifying the mixture. Because of continued flow of milk from below, the thin layer of milk along the side of the cylinder passes upward toward the outlet at the upper end of the cylinder. During the passage upward the milk is under centrifugal pressure of between 200 and 300 pounds to the square inch. In this upward passage any particles heavier than milk cling to the wall of the cylinder, thus producing a clarifying effect. The top of the cylinder is capped by a disk with small circular holes at its periphery. The milk leaves these holes at a pressure of 200 to 300 pounds to strike against the side of the receiving chamber, thus further emulsifying and homogenizing the product.

The "milk" produced by the mechanical cow, if sold, would be required to have a label declaration other than milk or in addition to milk. Though it may be prepared wholly from milk constituents which have been separated and remixed, the product is not milk under the legal definition of this term. The term "reconstituted milk" presumably is legally applicable.

In most respects the "milk" produced by the mechanical cow has all the food value of fresh milk. However, it is well known that the heat treatment incident to pasteurizing and drying causes decrease in thiamine and ascorbic acid content. An analysis submitted by the manufacturer indicates that no ascorbic acid is present in the final product and that a loss of approximately 15 per cent occurs in the thiamine content. A further loss of thiamine seems likely with storage of the dried milk. Despite these losses, the product has high nutritional value and nutritionally is an excellent substitute for milk.

The product of the machine has a low bacterial content when all instructions have been followed. The instructions include rigid cleanliness of the machine. It is the preference of the manufacturer that the butter and dried skimmed milk be obtained from him, thus possibly making more certain that the components of the product have a low bacterial content. Normally dried skimmed milk may be expected to have few living bacteria. The butter recommended is prepared from sweet pasteurized cream and is unsalted. Salted butter may be used by means of an additional centrifugal bowl which will produce a salt-free butter. The pasteurizing of cream for butter making is commonly carried out at a temperature higher than that used for the pasteurization of milk, thus tending toward a lower bacterial content. Starting with components having few bacteria, and with pasteurizing of the mixture at the beginning of the process, the bacterial content should compare favorably with that of good certified milk which has been pasteurized. The manufacturer states that under conditions of testing the average number of bacteria is approximately 100 to the cubic centimeter.

The manufacturer of the mechanical cow has foreseen a shortage of butter in various parts of the world and the lack of refrigerated shipping space for its transport. Vitamin fortified vegetable oil substitutes for butter have been devised which make a product acceptable as to taste and which can be shipped and stored more easily than butter. The "milk" prepared with such a butter substitute would be the equivalent of "filled milk." Though such a product would have many nutritional virtues, it is one which has little legal standing in this country. The Council on Foods and Nutrition cannot give its approval to illegal products.

The principle of production of "milk" by the mechanical cow merits approval when dried skimmed milk, butter and water are the ingredients. Dried skimmed milk and butter have keeping qualities not possessed by fresh milk. The machine is useful in supplying a good substitute for milk and cream. It is useful on ships and in regions where dairies are inadequate or nonexistent. Many such regions exist in this country, and their number has been increased because of war conditions. Since the product can be prepared under some circumstances at a cost somewhat less than that of fresh milk for retail distribution, conceivably it could enter into competition with fresh milk.

ACCEPTED FOODS

THE FOLLOWING ADDITIONAL FOODS HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON FOODS AND NUTRITION OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO ACCEPTED FOODS.

GEORGE K. ANDERSON, M.D., Secretary.

CANNED AND DRIED FRUITS AND FRUIT PRODUCTS (*See* Accepted Foods, 1939, p. 70).

Pasco Packing Association, Dade City, Fla.

OLD SOUTH BRAND CONCENTRATED ORANGE JUICE, a pasteurized orange juice concentrate formed by evaporating freshly expressed orange juice under reduced pressure to a Brix of 65 degrees. It is pasteurized, but the firm recommends that it be kept at a temperature of 45 degrees or less.

Analysis (submitted by manufacturer).—Moisture 28%, ash 1.8-2.0%, fat (ether extract) 1.0%, protein (N × 6.25) 5-6%, sucrose 28%, reducing sugar 28%, citric acid 3.9-6.0%, ascorbic acid 180-300 mg. per hundred grams, specific gravity 1.33.

Calories.—2.4 per gram; 68.16 per ounce.

Vitamin Claims.—Ascorbic acid (determined by the Dye method) on the basis of the median of range reported, using a dilution of 6½ additional parts of water (firm recommends addition of six or seven parts); the resulting drink contains 49.6 mg. of ascorbic acid per hundred cubic centimeters.

PREPARATIONS USED IN THE FEEDING OF INFANTS (*See* Accepted Foods, 1939, p. 156).

Gerber Products Company, Fremont, Mich.

GERBER'S CHOPPED VEGETABLE AND BEEF WITH RICE, consisting of potatoes, water, celery, beef, tomato pulp, carrots, rice, salt and onion powder.

Analysis (submitted by manufacturer).—Moisture 87.8%, ash 1.3%, fat 0.5%, protein (N × 6.25) 2.8%, crude fiber 0.4%, carbohydrates (by difference) 7.2%, Ca 0.018%, P 0.037%, Fe 0.0021%, Cu 0.00029.

Calories.—0.4 per gram; 13 per ounce.

Vitamins.—Protocols of vitamin assay (1941) show that this product contains 1,400 international units of vitamin A, 0.032 mg. of thiamine and 1 mg. of ascorbic acid for each hundred grams.

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SATURDAY, AUGUST 12, 1944

AID TO PHYSICALLY DISABLED

Plans are being formulated by a subcommittee of the House Committee on Labor, of which Congressman Kelley of Pennsylvania is chairman, for an extensive survey of the extent and character of aid given by the federal, state and local governments and by private agencies to the physically handicapped. This survey is to be conducted under authority of a House resolution adopted by the House of Representatives June 20. According to the chairman of the subcommittee, it was estimated that before Pearl Harbor some 800,000 people became physically handicapped each year. Since that time the number has increased greatly. The survey will be designed to explore the problem of unemployment of the physically handicapped persons in the United States, estimated at some 25,000,000, and to provide a means whereby Congress may be possessed of the requisite knowledge to deal with the problem. All categories of the physically handicapped, it is understood, will be covered by the study, including persons with amputated limbs and with cardiac disorders, victims of infantile paralysis, the blind, the deaf and the hard of hearing. The subcommittee, on the basis of information it obtains, is expected to submit a program to Congress for the assistance of the physically handicapped to the end that they may be profitably employed. The extent to which this program may involve an extensive health program for the physically disabled cannot at this time be accurately anticipated.

Proposals to amend the Social Security Act specifically to provide benefits for the adult physically disabled have been made from time to time. Several bills of this type are now pending in Congress before the House Committee on Ways and Means and the House Committee on Education. The Congress has only recently enacted broad legislation for the rehabilitation of disabled veterans, which program will be under the administrative guidance of the Veterans' Administration. It has also extensively revised the Federal Vocational Rehabilitation Act to provide for the physical restoration of civilians, and this program is being administered by the Federal Security Agency.

Chairman Kelley, in referring to the uncorrelated existing programs, said that at the present time something like eighteen different governmental agencies have something to do with the physically handicapped. The need for a consolidation of federal activities in the field of health and related fields has been recognized by the House of Delegates for many years. If the Kelley subcommittee will recommend that federal activities relating to the physically handicapped be consolidated in an appropriate federal agency, such as the Federal Security Agency, and if that recommendation is accepted by the Congress, another step will have been taken to effect a long delayed—too long delayed—simplification of federal participation in health and allied programs. Hearings will be scheduled by the Subcommittee to Investigate Aid to Physically Handicapped within the near future.

VIRULENCE OF PENICILLIN RESISTANT BACTERIA

Encouraging new data regarding the virulence of penicillin resistant staphylococci are reported by Spink and his associates [1] of the division of internal medicine, University of Minnesota Medical School. As a result of an inadequate therapeutic dose or of test tube exposure to nonsterilizing concentrations of penicillin, pathogenic bacteria may become penicillin resistant. This acquired resistance is a relatively stable hereditary characteristic of the micro-organisms, persisting through innumerable test tube generations. Generally it is assumed [2] that micro-organisms with this acquired penicillin resistance do not show other changes in their biologic and metabolic characters and thus constitute an additive epidemiologic danger.

Spink isolated four strains of coagulase positive staphylococci from osteomyelitic lesions in children, with a later duplicate strain from 1 child after it had received inadequate therapeutic doses of penicillin. The four strains thus obtained were approximately equal in their resistance to penicillin, growth being completely inhibited by the addition of from 0.04 to 0.06 Oxford unit per cubic centimeter of culture medium. The four strains were gradually adapted to penicillin by daily transfer to culture medium containing increasing concentrations. Control daily transfers in penicillin free medium were made with each strain. After a hundred or more serial transfers each strain had become penicillin resistant. With two of the strains complete

1. Spink, W. W.; Ferris, V., and Vivino, J. J.: Proc. Soc. Exper. Biol. & Med. **55**: 210 (March) 1944.
2. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardiner, A. D.; Heatley, N. G.; Jennings, M. H., and Florey, H. W.: Lancet **2**: 177 (Aug. 16) 1941.

inhibition of growth now required as much as 80 to 120 Oxford units per cubic centimeter, or 2,000 times the penicillin concentration necessary for complete inhibition of the parent strain. These two strains were transferred to veal-agar slants and placed in a refrigerator for three months, at the end of which period they showed no decrease in their acquired penicillin resistance.

The acquired penicillin resistance was associated with morphologic changes in each culture. Each resistant strain showed pleomorphism, with large spherical cell bodies quite apparent. Two of the parent strains produced a brown-orange pigment under certain culture conditions, which pigment was greatly decreased in amount in the homologous adapted strains. In four of the five adapted strains the rate of test tube proliferation was distinctly slower than with the parent culture. These facts suggest both a morphologic and a metabolic deterioration of staphylococci as a result of the acquired penicillin resistance, giving rise to the hope that the adapted strains are of reduced pathogenicity or virulence.

To test this hoped for loss of virulence Spink adopted a technic previously developed in his laboratory,[3] that of titrating the resistance of each strain against the bactericidal properties of defibrinated normal human blood. To each 0.5 cc. of fresh defibrinated blood there was added 0.1 cc. of a serial dilution of twenty-four hour broth cultures of the organism to be tested, seven 1:10 serial dilutions being tested with each strain. The approximate number of organisms thus added to each test varied from approximately 25,000,000 down to 25. The tubes were then sealed and rotated for forty-eight hours at incubator temperature, at the end of which time the contents of each tube were tested for sterility.

In a typical experiment the 25 penicillin susceptible staphylococci in the seventh tube failed to grow, while the first to sixth tubes did not become sterile. The 0.5 cc. blood sample used in this test was therefore able to kill between 25 and 250 penicillin susceptible staphylococci, or approximately 275 staphylococci per cubic centimeter. In a parallel test with a homologous penicillin resistant strain a duplicate human blood sample killed between 11,000 and 110,000 adapted staphylococci, or approximately 120,000 staphylococci per cubic centimeter. The penicillin resistant strain was thus four hundred times more susceptible to the bactericidal properties of human blood than the parent strain from which it was developed. Similar decreases in microbic vigor were demonstrated for all penicillin resistant strains thus far tested.

These results are in contrast to results of a parallel study of strains of staphylococci adapted to grow in the presence of sulfonamides. Defibrinated human blood has no greater bactericidal action on sulfonamide resistant strains than on the parent sulfonamide sensitive strains from which they were developed. If adequately confirmed, these results suggest that, while sulfonamide resistant strains of staphylococci may function as an additive epidemiologic danger, acquired penicillin resistance of staphylococci is of relatively little hygienic interest. No theory is as yet suggested to account for this difference. Whether or not the same difference is demonstrable in micro-organisms other than staphylococci has not yet been reported.

3. Spink, W. W., and Paine, J. R.: J. Immunol. **38**: 383 (May) 1940.

WORKMEN'S COMPENSATION FOR CANCER ASCRIBED TO SINGLE INJURY

Under workmen's compensation acts a claim that a workman has died or been disabled because of a cancer resulting from an industrial accident is decided in the first place by an industrial board or some equivalent tribunal. Such tribunals, even though without legally qualified physicians and lawyers among their members, have to decide questions of law and of fact as they arise and make their awards accordingly. The laws governing appeals from such awards vary in the different states, but in many states an appellate court may set aside an award or remand a case to the industrial board for further proceedings only because of errors of law. The board's findings as to fact are not open to review except that the appellate court may determine whether such findings are based as the law requires on reasonable evidence.

Whether or not a fatal or disabling cancer was caused by an industrial accident is certainly a question not of law but of fact. If reasonable evidence has been introduced in the proceedings before an industrial board to sustain a finding that an industrial injury, single or multiple, has caused a cancer that resulted in disability or death and the industrial board so decides, an appellate court in any state in which the general rule laid down above is in force cannot set aside the award or remand the case for further proceedings, even though the court believes that the weight of all the evidence in the case did not justify the decision.

Appeals from decisions of industrial boards and similar tribunals awarding compensation for death or disability attributed to cancer supposed to have resulted from industrial accidents seem to be, therefore—in most states, at least—hardly a satisfactory remedy for errors of judgment in making such awards. Rather it would be better, without denying that a cancer may be caused by a single injury, to organize our industrial boards so as to enable them better to weigh the medical evidence that comes before them. This suggestion should not be construed as a reflection in any way on the work

of such boards, for with the aid of their medical assistants their work is, it is believed, generally well done. As a further means of avoiding injustice in the making of awards, appellate courts should be vested with the right to set aside or to remand for further proceedings cases in which decisions seem to be clearly contrary to the weight of the entire evidence even though there may be some reasonable evidence to support them.

In any event, as long as the cause or causes of cancer are not known, as long as there may be an opinion among the medical profession at large to the effect that a single trauma may cause cancer and as long as physicians are willing to testify under oath that in their professional opinions a single trauma can cause and has caused cancer in the case before the industrial commission, industrial commissions cannot be blamed if sometimes they accept such evidence and grant awards accordingly.

In forming his opinion in a given case the physician should bear in mind the lack of definitive knowledge with regard to the relation of a single injury to the causation of cancer. Whether human cancer can be caused by a single accidental injury remains an open question. The results of clinical observations on the question are not conclusive. While authentic cases are recorded in which cancer arose at the site of an injury, the possibility that it was under way before the injury was received or that it developed independently of the injury cannot be excluded. That cancer can and does arise independently of injury and that single injuries become associated with cancer in one way or another only in extremely few cases will not be denied. As far as known, cancer in animals has not been produced experimentally by single mechanical injury.

Current Comment

PENICILLIN AS AN INHALANT

Under the auspices of the Long Island Biological Association Bryson, Lansome and Laskin [1] studied the behavior of penicillin as an inhalant. With a standard glass nebulizer a solution of the sodium salt of penicillin was readily nebulized for inhalation. Experiments on rabbits and on human beings demonstrated that in such form penicillin passed through the respiratory tract and appeared in the urine. In rabbits penicillin was recovered from the lung tissue after inhalation. As penicillin is bacteriostatic for pneumococci, streptococci and staphylococci in extremely high dilutions, its inhalation as an aerosol may be of advantage in the treatment of respiratory infections with these and perhaps also other bacteria. The results of further experiments will be of interest. The question also arises whether penicillin will be of value as an air disinfectant.

1. Bryson, V.; Lansome, E., and Laskin, L.: Aerosolization of Penicillin Solutions, Science **100**: 33 (July 14) 1944.

CLEVELAND HEALTH MUSEUM

Many museums in the United States are contributing greatly to health education of the public. Some of these museums present their health exhibits in cooperation with local medical societies, while others operate under the guidance of physicians interested in health education. The Cleveland Health Museum has shown leadership in this field, and the medical profession has had a large part in its success. Organized under the auspices of the Cleveland Academy of Medicine to serve the people of Cleveland, the museum is rapidly becoming a national institution. Its exhibits have been used in seventeen states of the Union, as well as in Canada and Mexico. Health educators from various parts of the United States and from the Latin American countries have taken advantage of the intern training in visual health education offered by the museum staff. The appointment of a National Advisory Council indicates a further extension of these activities.

FOUR GENERATIONS OF SACROILIAC ARTHRITIS

Among disorders which involve the joints, the importance of heredity is recognized only in gout, rheumatic fever and probably certain degenerative forms of joint disease. An analysis of the exact mechanism played by genetics is difficult, however. Indeed, this has not yet been clarified even in gout and gouty arthritis, in which hereditary influences appear especially strong. Now Stauffer and Merrihew [1] show the pedigree of a form of arthritis that was present in a family in western New York State for at least four generations. The pedigree shows 22 affected persons in these four generations with a ratio of 21 arthritic persons to 12 normal (when siblings not old enough to have developed the disease were eliminated). All of the affected persons suffered pain in the sacroiliac region, and some also had sciatic pains and tingling and swelling of the extremities. The data for this study were collected by personal interview with affected and unaffected members of the family, most of whom were still living. The condition was encountered for the most part either in persons who were somewhat obese or who performed work of a manual nature. This suggests that the strain imposed by overweight or by the exertion from lifting may be direct factors in the onset of pain. The presence of excess uric acid in the urine in some persons, as well as symptoms of kidney disease, suggested to the writers that renal defects were present, but whether these were basic or merely symptomatic could not be decided. Possibly, these workers suggest, the basic action of the gene is to influence purine metabolism, and the renal disorder is secondary. If this should be the case, the disease in this family would appear to be more closely allied to the arthritis of gout than to any other form of joint disease. Whether this is correct or not, the writers feel confident from the similarity of symptoms in the afflicted members of the family reported that the disease is a genetic entity and the mechanism of inheritance is probably dominant.

1. Stauffer, James, and Merrihew, N. H.: A Pedigree of Sacroiliac Arthritis, J. Heredity **35**: 112 (April) 1944.

MEDICINE AND THE WAR

DEFERMENT OF PREMEDICAL AND MEDICAL STUDENTS

Following is the reply of Major General Hershey, Director of the Selective Service System, to a memorandum submitted to him by Senator Lucas of Illinois, and comments on General Hershey's letter by the Council on Medical Education and Hospitals of the American Medical Association:

NATIONAL HEADQUARTERS
SELECTIVE SERVICE SYSTEM
21st Street and C Street NW.
Washington 25, D. C.

July 24, 1944.

The Honorable Scott W. Lucas,
United States Senate.

Dear Senator Lucas:

This will acknowledge your memorandum of July 15, 1944.

A survey made at this Headquarters indicates that there is undue concern over the future supply of doctors. The military forces demand medical attendance out of proportion to that demanded by the civilian population, and, during this period of emergency, civilian medical attendance, like everything else, must be limited to necessity. After the war there will be an adequate number of physicians, for there are now in the medical schools a number of students greater than the number which ordinarily study medicine in peacetime. In the accelerated program it is expected that all of these will finish their internships and be ready for practice by 1949. Our investigation revealed that we will then have not less than 193,000 doctors in the population as a whole. There will be one physician for approximately each 733 persons. The publications of the American Medical Association indicate that there was one doctor for each 765 persons in 1938, when the last figures were made public. Our figure for 1949 is based on a population estimation made at this Headquarters and by adding students now in college and to be graduated before 1949 to the American Medical Association's 1944 figures, less the expected attrition. The increased need for physicians is recognized, but it would seem that this excess over our past requirements would be adequate to meet future demands.

The concern is principally over the future shortage of doctors because it is alleged that no premedical students are being educated for the freshman classes to enter medicine in 1945. The question of the deferment of preprofessional students has been given much consideration. The armed forces have provided for the utilization of 53 per cent of the capacity of the classes in medical schools in 1945. This leaves only 47 per cent of the capacity which may be filled by civilian students. To find the number to prepare in premedicine and to fill these vacancies there is available a large number of men between 18 and 26 years of age found physically disqualified for any military service or physically qualified for limited military service only; women; soldiers discharged from the Army, and men over 30 years of age. Those men found physically disqualified for military service are frequently disqualified by reason of conditions which will not prevent them from being eligible for the study of a profession. It is incumbent upon the educational institutions to find in this group the men they want, and to offer them the inducement necessary to get them to study the professions.

Any additional students who are necessary to qualify for entrance into the medical, dental, osteopathic and veterinarian schools should be taken from the armed forces and from those who have spent at least two years in active service. The morale of the country will be definitely injured by continuation of a policy which will permit a boy becoming 18 to enter successively preprofessional and professional schools without fulfilling any military obligations. An application of this system will be equally injurious to the medical, dental, osteopathic and veterinarian professions. This is true, first because men will become doctors, missing the major civic experience of this age for young men. The professions will be the poorer because they will find that they have doctors who are immature in years as well as in experience, and whose professional information was acquired in accelerated courses both in preprofessional schools and professional schools. This can be avoided by the selection of competent, mature, experienced men who have fulfilled their duties of citizenship to their country in war.

Dr. Willard C. Rappleye, Chairman of the Executive Council, Association of American Medical Colleges, Dr. A. W. Bryan, President, American Association of Dental Schools, and Mr. William N. Hodgkin, Chairman, Council on Dental Education, American Dental Association, have recommended to me that the Army and the Navy demobilize, either by furlough to the Reserve or by discharge, men selected because they have had at least two years of military service, have had preprofessional training to a degree which will make it possible in a nine month course to prepare them for entrance into the professional schools, and who are anxious to enter the professions under discussion. This plan was submitted to the Secretary of War and the Secretary of the Navy in an identical letter on June 6, 1944. A joint reply was received on June 29, 1944, indicating that the recommendation had not been favorably considered.

I am firmly of the opinion that the project submitted by Dr. Rappleye, Dr. Bryan and Mr. Hodgkin furnishes the only satisfactory solution to this problem if additional students are required for the preprofessional schools.

We are returning the attachment which accompanied your memorandum.

Sincerely Yours,
LEWIS B. HERSHEY,
Director.

Comment by Council on Medical Education and Hospitals

There are four major points made in General Hershey's letter which may be seriously questioned on the basis of information collected by the Council on Medical Education and Hospitals from the schools of medicine of this country:

1. "There is undue concern over the future supply of doctors." It is also stated that there will be more doctors available after the war than before the war. This is not all clear. In the first place, significant numbers of the physicians in the United States do not directly participate in providing medical care. These physicians are otherwise engaged or retired. Therefore physician-population ratios cannot be computed from the total number of physicians. The figures pertaining to increases or decreases in physicians available to civilians in the next few years are plain. Under the accelerated program there were 10,357 graduates from July 1, 1942 (when acceleration started in most schools) to June 30, 1944. Based on figures submitted by each school, it is estimated that an additional 9,844 will graduate from July 1, 1944 to June 30, 1945. This totals 20,201 graduates during a complete three calendar year cycle involving four graduating classes. If acceleration is continued even though admissions are made annually, there will be an additional approximately 20,000 graduates in the ensuing three year cycle from July 1, 1945 to June 30, 1948.

During this whole six year accelerated period there should be approximately 40,000 graduates. During the six prewar

years July 1, 1935 to June 30, 1941 there were 31,215 graduates. All other things being equal, these figures would indicate an increase in the physician population by 8,785 in 1948.

But all other things will not be equal. This entire surplus physician population would be absorbed by a standing army of 1,757,000 men at 5 medical officers per thousand men. Should the standing postwar navy require 5,000 physicians and the Veterans Administration 10,000, the physician population available to civilians would actually be reduced by 15,000 instead of increased.

In these calculations no account is taken of general population increases, fatalities and incapacitating injuries among medical officers in service, the current increased death rate among physicians, increasing demands of the civilian population for improved medical care, requirements for American physicians in the rehabilitation of liberated countries and the possible permanent damage of some of the "plant" of medical education through possible failure of some schools to continue operation with greatly reduced enrolments. Concern over the future supply of doctors is fully warranted under these conditions.

2. ". . . Forty-seven per cent of the capacity (of entering classes) . . . may be filled by civilian students (in 1945)." The deans of all medical schools were asked "How great a reduction do you estimate there might be in your 1945 entering classes if you are forced to select 41 to 47 per cent civilians, with no selective service deferments?" In response, the deans of only nine schools thought they might be able to fill civilian places under these conditions. Fifty-seven schools estimated reductions of from about 10 to over 40 per cent in freshman enrolments. There was an average reduction of 23 per cent for the sixty-six schools venturing estimates. The remaining eleven schools were unwilling or unable to estimate reduction which will occur.

It should also be recalled that the provisions of the current army appropriation bill, by abolishing further admissions of trainees to the A. S. T. premedical program, increase to 70 or 75 per cent the number of students which must be obtained from civilian sources in 1946.

3. Students are available from "a large number of men between 18 and 28 years of age found physically disqualified . . .; women; soldiers discharged from the Army and men over 30 years of age." These possible sources were taken into consideration in the estimates of reduced enrolments made in the preceding paragraphs. It is extremely doubtful whether qualified students in these categories are available in significant numbers at present unless admission standards are drastically reduced. There is no evidence of the existence of a large reserve pool of qualified women. Some physically disqualified and discharged men might be physically able to study and practice medicine, but these occupations are arduous, requiring vigorous health, and are not for the physically unfit. Many of those discharged are sufficiently unstable emotionally to prevent their becoming good doctors. Also there is no doubt that this group includes many men who have been previously rejected for admission to medical schools because they failed to meet admission standards, even though they may have pursued premedical studies before the war. While every favorable consideration should and will be given to medical school applications from veterans, it would serve neither the veteran nor the public to admit to medical schools men who do not possess the requisite physical, emotional, mental and other qualifications.

It will not meet the problem of obtaining students from these groups "to offer them the inducement necessary to study medicine." Students are impelled to study medicine through a long and complicated series of circumstances involving their whole past education, drives, capacities, emotional and social experiences, and not by offering special inducements.

4. "Additional students . . . should be taken from . . . those who have spent two years in active service." Much of what has been said above applies to this suggestion. Even if the Army and Navy had not rejected this plan, it probably would have resulted in many men being returned from the widespread theaters of military operations and even from this country, who would not possess the qualifications for the study of medicine. The commanding officers in Asia and Africa and Italy and France, or even the United States, with their many heavy responsibilities and inexperience in selection of medical students would be scarcely in a favorable position for collaborating with deans many miles away in assigning capable men to medical studies.

ARMY

PROCEDURES GIVEN FOR A. S. T. P. MEDICAL, DENTAL PROGRAMS

Procedures for disposal of certain enlisted personnel in the Army Specialized Training Medical Program necessitated by provisions of the Military Appropriations Act, 1945, have been announced by the War Department. The act, approved June 28, 1944, stipulated that none of the funds appropriated shall be used for training medical and premedical students unless they were in training prior to June 7, 1944, and such training was defrayed from 1944 appropriations.

At the same time, it was announced that the A. S. T. P. dental training program is being terminated at the close of the present semester except for those in the senior, or final, year, who will be permitted to complete the course and on graduation will be commissioned. This action is taken because the Army's requirements for dentists are now filled.

Those individuals now on active duty whose medical or premedical educational expenses were defrayed in whole or in part by the government under the A. S. T. P. program prior to June 7, 1944 will be continued in the medical program of the A. S. T. P. Those on active duty whose medical or premedical training was not defrayed either in whole or in part under the A. S. T. P. program prior to June 7, 1944 and who for that reason cannot be continued in the training program fall into two classes who will be disposed of as follows:

1. Those who have letters of acceptance and who would have entered an accredited medical school by Dec. 31, 1944. An individual in this group may elect to be discharged from the Army shortly before the entrance date of the class for which he was accepted; or to be assigned to the Medical Department with no further A. S. T. P. medical training.

2. Those who do not have a letter of acceptance to an accredited medical school, for entrance by Dec. 31, 1944. These men will be continued on active duty and will not be eligible for A. S. T. P. medical training.

COMMANDING OFFICER AT HALLORAN APPOINTED BRIGADIER GENERAL

Halloran General Hospital, Staten Island, N. Y., was the recipient of one of the most signal honors in its distinguished history as an army hospital when Col. Ralph G. DeVoe, commanding, was promoted to Brigadier General May 24. The June 30 issue of the *Halloran Beacon*, Post Publication at Halloran General Hospital, is a tributary volume to Brigadier General DeVoe.

Brigadier General DeVoe graduated from the University of Pennsylvania School of Medicine, Philadelphia, in 1908 and from the Army Medical School in 1910. Before World War I broke out he was stationed in the Philippines, where he was promoted to captain in 1913. He became a first lieutenant in the Medical Reserve Corps in 1919 and was promoted to major on May 15, 1917. In September 1917 he became commanding officer of Base Hospital 34 in Nantes, France, and in November 1918 he was made commanding officer of the Hospital Center in Nantes. For this service he was awarded the decoration of Chevalier of the Legion of Honor by the French government, and on May 5, 1919 he became a colonel in the Medical Corps of the U. S. Army.

NAVY

HOSPITALIZATION OF DEPENDENTS OF NAVAL PERSONNEL

Instructions have been issued by the Navy Department to govern the hospitalization of dependents of naval personnel in accordance with the act of May 10, 1943, which provided for expansion of facilities for hospitalization of dependents of naval and Marine Corps personnel. The instructions, dated June 10 but just published, define dependents as wife, unmarried dependent children under 21 years of age and mother and father if in fact dependent. Widows of deceased naval and marine personnel also are entitled to hospital care in the same manner as dependents. The Navy Department has authority to designate naval hospitals to which dependents shall be admitted and may remove such designation or add to the list of designated hospitals at any time. The commanding officer of the designated hospital shall determine the availability of accommodations for dependents and their need for hospitalization, reserving sufficient facilities for present and prospective naval personnel patient loads. Dependents shall be admitted only for acute medical and surgical conditions, exclusive of nervous, mental or contagious care. Dental treatment shall be administered only as an adjunct to inpatient hospital care and shall not include dental prosthesis or orthodontia. For each patient admitted and for each day in the hospital, the member of the Navy or Marine Corps concerned shall pay $7.75. While the Coast Guard is operating as part of the Navy, dependents of Coast Guard personnel are entitled to hospitalization on the same basis as members of the other sea services.

NAVY AWARDS AND COMMENDATIONS

Captain Jesse D. Jewell

The Navy Cross was recently awarded to Capt. Jesse D. Jewell "for distinguished service in line of his profession, extraordinary courage and disregard of his own condition during an attack on the fleet in Pearl Harbor on Dec. 7, 1941. Although burned about the face and arms from fires nearby his station on board the U. S. S. *California*, he continued at his post of duty and administered effective first aid." Dr. Jewell graduated from the University of Oregon Medical School in 1918 and entered the service in July 1921. He is now executive officer of the U. S. Naval Hospital at Corona, Calif.

PROMPT EVACUATION OF CASUALTIES GREATEST SINGLE FACTOR IN SAVING LIVES

Medical officials at Saipan, Marianas Islands, believe that the greatest single factor in saving the lives of wounded Marines on this island is the prompt evacuation of casualties to mobile field hospitals close behind the front. At one of these hospitals, with Comdr. R. L. Sharp, formerly of Morristown, N. J., in charge, it was revealed that fewer than 1 per cent of all casualties brought to the hospital prove fatal. "If a man is not killed instantly, and if he can be brought to us within an hour or so after being wounded we can almost guarantee to save his life," Dr. Sharp stated. The average time for evacuating a casualty is about an hour, he said. Ambulance jeeps go as close to the front as practical, and stretcher teams working in relays carry the wounded to the jeeps, and they are usually on the operating table within an hour after being picked up. Five doctors, including a surgeon, an orthopedic specialist and a dentist are on hand at all times. They are assisted by 75 Navy pharmacist's mates and 25 Marine orderlies. The hospital is equipped with 100 beds and a surgical ward which includes an x-ray machine and special operating instruments. It maintains its own sanitary cooking galley, so that special diets can be prepared when necessary. Patients are returned to the rear lines as quickly as practicable to make room for new casualties. "While the sulfonamide drugs have done wonders in preventing infection and plasma has performed miracles in overcoming shock, it is speedy evacuation that really saves lives," Dr. Sharp said. "Sulfonamides, plasma and evacuation," he emphasized, "are like the legs of an equilateral triangle, each dependent on the others."

MISCELLANEOUS

HOSPITALS NEEDING INTERNS AND RESIDENTS

The following hospitals have indicated to the Council on Medical Education and Hospitals that they have not completed their house staff quota allotted by the Procurement and Assignment Service:

(Continuation of list in THE JOURNAL, July 29, page 918)

CALIFORNIA

Santa Clara County Hospital, San Jose. Capacity, 470; admissions, 4,435. Dr. Henry E. Dahleen, Superintendent (resident—tuberculosis).

CONNECTICUT

The Meriden Hospital, Meriden. Capacity, 139; admissions, 3,802. Dr. Herbert T. Wagner, Medical Director (interns—October 1).

Waterbury Hospital, Waterbury. Capacity, 372; admissions, 8,144. Miss Aida E. Creer, R.N., Superintendent (resident—October 1).

LOUISIANA

T. H. Schumpert Memorial Hospital, Shreveport. Capacity, 120; admissions, 3,681. Sister Mary Celestine, Superintendent (intern).

MINNESOTA

University Hospitals, Minneapolis. Capacity, 450; admissions, 9,187. Mr. Ray M. Amberg, Superintendent (resident—orthopedics, August).

NEW YORK

Israel Zion Hospital, Brooklyn. Capacity, 380; admissions, 10,532. Dr. J. Prager, Executive Director (interns—October 1944, January 1945).

St. Mary's Hospital, Brooklyn. Capacity, 328; admissions, 5,004. Sister Mary Helen, Superintendent (interns).

Mount Vernon Hospital, Mount Vernon. Capacity, 254; admissions, 5,749. Mr. Arthur B. Solon, Superintendent (interns—October 1).

Beth David Hospital, New York. Capacity, 150; admissions, 3,985. Mr. Harold Salkind, Executive Director (interns).

New York Post-Graduate Medical School and Hospital, New York. Capacity, 409; admissions, 8,622. Dr. William B. Talbot, Medical Superintendent (resident—urology).

OKLAHOMA

St. John's Hospital, Tulsa. Capacity, 273; admissions, 10,327. Sister M. Olga, Superintendent (interns).

WEST VIRGINIA

St. Francis Hospital, Charleston. Capacity, 118; admissions, 4,923. Sister Mary Paul, Administrator (2 residents—mixed, October 1).

PHYSICIANS PHYSICALLY DISQUALIFIED SINCE JULY 1943

An agreement has been reached with the Surgeons General of the Army and Navy that: 1. Physicians who have been physically disqualified for service in the armed forces since July 1943 and who are now serving in an essential capacity as an intern, resident, teacher or other hospital appointee will not be asked to submit to reexamination or to activate or reapply for a commission without a standard form 97 indicating that they are currently available. 2. Physicians physically disqualified for service in the armed forces and now in essential hospital positions who are being reconsidered for a commission in the armed forces will not be called to active duty until the expiration of their present obligation, provided form 218 for each physician is submitted covering such period of service.

ORGANIZATION SECTION

WASHINGTON LETTER

(From a Special Correspondent)

July 7, 1944.

American Academy of Pediatrics Withdraws Support from Children's Bureau

Further evidence of opposition to a trend toward socialized medicine was noted here in the action of the American Academy of Pediatrics in withdrawing its support from the Children's Bureau because its system of emergency maternity and infant care is an entering wedge for socialized medicine.

Last month a conference of child specialists and social workers here took a stand against the bureau's group care of children, asserting that group care was damaging to child welfare and actually more expensive than a foster family system of care which the conferees advocated. The academy announced its position in the *Journal of Pediatrics* as follows: "We feel the time has come when the academy and the pediatricians of the United States must withdraw their support from the Children's Bureau and use their influence as a group and as individuals to place all health activities under the Public Health Service."

Records of the Children's Bureau show that since the beginning of the program in March 1943 through May 1, 355,000 mothers and babies of servicemen received federal aid under the program for which Congress appropriated $42,800,000. Entitled to care under the program are wives and infants of men in the four lowest paid grades of the armed forces.

The academy withdrew its support despite insistence of Dr. Martha M. Eliot, assistant chief and chief medical adviser of the bureau, that "EMIC will disappear when the war is over."

The pediatricians, in throwing their support from the Children's Bureau to the Public Heatlh Service, are transferring it from an agency dominated by social workers to the medical authorities wielding balance of power at Public Health Service.

Dr. Eliot says in defense of the program that Congress brought it into existence as a wartime measure. She denied that the Children's Bureau intended to enter the practice of medicine after the war or to continue the emergency medical and infant care program in some other guise.

Pediatricians argue that the wartime program had made the Children's Bureau an active factor in the practice of medicine in this country "dictatorially regulating fees and conditions of practice on a federal basis." It quoted articles issued by the bureau as indicating that it is evident that "a free to all service, with full time salaried physicians, paid for directly from general taxes and controlled and directed by a federal bureau," is planned. The average EMIC payment is reported to be about $84 a case.

National War on Tuberculosis

The ninety-two United States cities of 100,000 or more population will be major battlefields of the war on tuberculosis to be waged under the national tuberculosis control program, for which some $10,000,000 was authorized. About one out of every three tuberculosis deaths occurs in these cities, and the average tuberculosis death rate in them is about one third higher than in smaller towns and rural areas.

In making this announcement, Dr. Herman E. Hilleboe, chief of the U. S. Public Health Service Tuberculosis Division, said that tabulations based on census figures for the 1939-1941 three year period show variations in tuberculosis death rates of cities ranging from as low as 15.6 per hundred thousand among white in Grand Rapids, Mich., to as high as 275.5 per hundred thousand among nonwhite persons in Newark, N. J. A survey showed tuberculosis to be three times as fatal to the nonwhite as to the white, according to death rate figures. Women living in country areas were said to be more susceptible to the disease, although death rates were higher among men in metropolitan than in rural areas.

Syphilitic Registrant Reclaimed by Treatment

Of more than a quarter million Selective Service registrants reclaimed for military duty after blood tests indicated that they were infected with syphilis, some 125,000 have already enlisted or have been inducted into the armed forces and 140,000 more are available unless otherwise disqualified. These figures, announced by the U. S. Public Health Service, are based on tabulations of data up to June 30, 1943 from twenty-two states, on 182,607 of the 720,000 registrants with evidence of syphilis. Symptomatic evidence of syphilis was reported as having been revealed among 720,000 of the first 15,000,000 registrants given blood tests for syphilis. The job of tracing, treating and inducting a large number of the infected registrants was accomplished by cooperation among Selective Service boards, state and local health departments, the Army and the Navy.

Nurse Corps Seeks 60,000 More Cadets

In calling for enrolment of at least 60,000 more cadets this year to meet increasing needs for hospital personnel, the U. S. Public Health Service paints a bright postwar future for girls joining the U. S. Cadet Nurse Corps. They will serve a vital war purpose in preventing closing of wards and curtailment of hospital services, with virtually all hospitals extremely short handed. After the war, many new fields are expected to be open to women in the nursing profession, the following being cited as possibilities: expansion of community health services, widening of group hospitalization and developments in industrial safety and first aid programs.

WOMAN'S AUXILIARY

Indiana

At a recent meeting of the Clark County Auxiliary, "Cancer Control" and the Wagner-Murray-Dingell bill were discussed.

Pennsylvania

The Philadelphia County auxiliary distributed 6,000 copies of the Wagner-Murray-Dingell bill arranged by Dr. Francis F. Borzell. During the present year the auxiliary gave $1,300 to the Aid Association of the Philadelphia County Medical Society and $200 to the benevolent fund of the state society. The fourteenth annual health institute was held in April in the Philadelphia County Medical Society building, with fifty-three organizations participating.

The Philadelphia auxiliary celebrated its nineteenth birthday April 14. Mrs. Lownes, the president, presented a memory book to the auxiliary containing the names of the past presidents. Nine past presidents were present and received pins of service.

Texas

The Dallas County auxiliary held its annual guest day meeting April 5.

Mrs. T. H. Thompson, publicity chairman for the Texas auxiliary, states that each auxiliary in the state has had one or more programs on the "Wagner-Murray-Dingell bill to show the evils of socialized medicine."

Wisconsin

One hundred members of the Milwaukee auxiliary attended the March meeting. Dr. L. J. Van Hecke spoke of the work done in cancer control by the Woman's Field Army, and Dr. E. H. Rynearson of the Mayo Clinic discussed "Obesity, the Unpopular Subject."

Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

CALIFORNIA

The Doctor Speaks to the Attorney.—A joint committee composed of three members of the Los Angeles Bar Association and three members of the Los Angeles County Medical Association are arranging a program on the theme "The Doctor Speaks to the Attorney." The series of lectures will begin in September and be concluded in December, covering various medicolegal problems with the medical factors emphasized from the point of view of different specialists. Legal members of the arranging committee are Messrs. F. Murray Keslar, John P. McGinley and Elbert H. Tilson; medical members are Drs. Fred B. Clarke, Long Beach, John Severy Hibben, Pasadena, and Louis J. Regan.

Cancer Prevention Clinic.—A clinic has been opened in Los Angeles to be known as the Cancer Prevention Society. It will be staffed by the Medical Women's Society of Los Angeles County on a voluntary basis and work in cooperation with the Women's Field Army. An announcement indicates that the clinic will be devoted to research. It was stated that "500 non-ailing women" will be asked to sign up for two complete physical examinations a year. No treatment will be given at the clinic, but if a woman is found to have any disease she will be referred to her family physician. Dr. Elizabeth Mason Hohl, educational director of the Women's Field Army in Los Angeles, is in charge of the clinic.

DELAWARE

New Health Commissioner of Wilmington.—Dr. Arthur Parker Hitchens, professor of public health and preventive medicine, University of Pennsylvania School of Medicine, Philadelphia, has been appointed health commissioner of Wilmington, according to *Philadelphia Medicine*.

ILLINOIS

Changes in Health Officers.—Dr. Samuel N. Mallison has been appointed to the new position of superintendent of health of the city of Decatur. Dr. Mallison will be in charge of the public health work of the city and assume much of the work formerly handled by Dr. Pierre A. Steele, city commissioner of public health and safety.

Chicago

Peoples Hospital Closed.—The Chicago Board of Health on July 18 closed the Peoples Hospital because of its insanitary condition and faulty record keeping, newspapers report. It was stated that the procedure was carried out in connection with an investigation by the state's attorney's office of an alleged adoption racket.

Changes on the Faculty at Illinois.—Dr. Raymond B. Allen, dean, University of Illinois College of Medicine, announced July 31 a number of changes on the medical faculty, among others, effective September 1:

Dr. Julius Hays Hess, who has been a member of the faculty for thirty years, retiring on account of age, as professor and head of the department of pediatrics. He will carry the title professor emeritus.

Dr. Henry George Poncher promoted to professor and head of the department of pediatrics to succeed Dr. Hess.

Dr. Milan Vaclav Novak to professor and head of the department of bacteriology and public health.

Dr. Yngve Joranson to associate professor emeritus, department of anatomy.

Dr. Aaron Arkin to professor, department of medicine (Rush).

Dr. Richard Leos Jenkins to acting head and associate professor of psychiatry.

Chester William Darrow, Ph.D., to associate professor, department of criminology, social hygiene and medical jurisprudence.

Dr. Norris Julius Heckel, to associate professor, department of surgery.

Dr. John Michael Dorsey to assistant professor, department of surgery (Rush).

Dr. Noah D. Fabricant to assistant professor, department of laryngology, rhinology and otology.

Dr. Edward A. Piszczek to assistant professor, department of bacteriology and public health.

James Clarence Flagge, Ph.D., to assistant professor, department of anatomy.

Dr. John Van Prohaska to assistant professor, department of surgery.

Dr. Anita E. Rapoport to associate and associate anesthetist, department of surgery and Research and Educational Hospital.

Dr. Boris S. Ury to associate, department of psychiatry.

KANSAS

Personal.—Dr. Chester E. Joss, Topeka, was elected president of the Kansas State Board of Medical Registration and Examination at its meeting in Topeka, June 8, succeeding Dr. Mirl C. Ruble, Parsons, who continues as a member of the board.

Special Society Elections.—Paul Haney, director of the division of sanitation of the Kansas State Board of Health, was chosen president-elect of the Kansas Public Health Association at its annual meeting in Topeka, June 6-8. Leon R. Kramer, D.D.S., director of the dental hygiene division of the state board of health, was installed as president and Dr. James E. Wolfe, Wichita, was named vice president. Miss Jane Taylor, venereal disease control nurse of the state board, is the secretary.——Dr. Clay E. Coburn, Kansas City, was chosen president of the Kansas Tuberculosis and Health Association at its annual meeting, June 6-8, in Topeka. Drs. Frank A. Trump, Ottawa, and Mrs. Mary C. Bure, R.N., Kansas City, are vice presidents. Theo C. Mueller, Topeka, is the treasurer, and Dr. Charles H. Lerrigo the executive secretary. All officers were reelected with the exception of Mrs. Bure.

KENTUCKY

Director of Tuberculosis Control Named.—Dr. Russel E. Teague, Louisville, has been appointed director of tuberculosis control for the Kentucky State Department of Health, succeeding Dr. John B. Floyd, Louisville, who resigned to become medical superintendent of a coal company at Stone, it is reported. Dr. Teague will be succeeded in his position as director of venereal disease control by Dr. Robert H. English, Hopkinsville, acting director of the Christian County department of health.

Silicosis Examining Board Created.—The recent establishment of a permanent medical examining board, paid by the state, to examine all claimants alleged to have become disabled by reason of silicosis has been announced. The board consists of two radiologists and one chest physician, namely Drs. Isaac T. Fugate, Louisville, for a three year term, Charles C. McCoy, Louisville, for two years and Thomas Atchison Frazer, Marion, for one year. The silicosis law in Kentucky was rewritten after a survey by the state department of health, representatives of the Associated Industries of Kentucky, representatives of the two national unions, the insurance carriers and employers groups. The new law is just now going into effect, according to Dr. Walter E. Doyle, Louisville, director of the state bureau of industrial hygiene, July 27. All cases will be referred first of all to the examining board for diagnosis. The results of the board will be referred back to the workmen's compensation board, which operates under the department of industrial relations for action. The law permits a finding of partial permanent disability and also contains a "second injury clause."

MAINE

State Medical Election.—Dr. Adam P. Leighton, Portland, was chosen president-elect of the Maine Medical Association at its annnal meeting in Rockland, June 26, and Dr. Raymond V. N. Bliss, Blue Hill, was inducted into the presidency. Dr. Frederick R. Carter, Portland, was reelected secretary.

MICHIGAN

Dr. Ryan Placed in Charge of Rapid Treatment Center.—Dr. Nelson W. Ryan has been assigned by the U. S. Public Health Service to the Michigan Department of Health to be in charge of the venereal disease rapid treatment center opened in June in Ann Arbor (THE JOURNAL, May 20, p. 220). Buildings for the center have been made available at the University Hospital. Dr. Ryan, who was in charge of the first rapid treatment center when it opened in South Carolina, has been associated with Dr. Udo J. Wile, professor of dermatology and syphilology at the University of Michigan Medical School, Ann Arbor.

Personal.—Dr. Henri Belanger was honored at a dinner, June 7, by friends and colleagues in recognition of his completion of fifty years in the practice of medicine, all of which time was spent in River Rouge. Dr. Belanger was presented with a gold writing set.——Dr. Edward Sawbridge, who began the practice of medicine at Stephenson in 1883, has retired as agent for the Michigan Bell Telephone Company at Stephenson, a connection he had held since 1890. Newspapers reported

that it was in Dr. Sawbridge's drug store in 1890 that the first telephone instrument was installed at Stephenson.——Dr. and Mrs. David H. O'Donnell, Detroit, celebrated their golden wedding anniversary, June 21.——Dr. Clark D. Brooks, a member of the Detroit Board of Education since 1939, has been elected president of the board.

Typhoid Carriers.—The Michigan Department of Health, Lansing, has under its supervision 290 typhoid carriers. In 1943 11 carriers were released from the department's supervision. One recovered spontaneously, 1 recovered following removal of the gallbladder, 3 moved to other states and 6 died. During 1943 21 new typhoid carriers were identified and placed under supervision; 19 of these were discovered as the source of new cases, while the other 2 were found through convalescent follow-up. No typhoid patient is released from supervision until three specimens, taken a week apart, are free from typhoid germs. Persons who continue to have the germs for a year are considered chronic carriers. In ten years in Michigan only 3 chronic carriers cleared up spontaneously.

Medicine in Survey of Public Opinion.—The Michigan Health Council is conducting a survey of public opinion in Michigan to obtain the attitude of the public toward the medical profession and hospitals, the cost of medical and hospital care, the attitude of the public regarding prepayment health plans under the auspices of professional groups, government or other agencies, and other related matters. The results will be used to formulate a program to educate the public in the type of service being provided by the doctors and doctors' agencies within the state. The Michigan Health Council was organized at a meeting in Mackinac Island, July 16-17, 1943 to act as a clearing house on matters of mutual interest for the Michigan State Medical Society, the Michigan Hospital Association, the Michigan Medical Service and the Michigan Hospital Service. Dr. Andrew S. Brunk, Detroit, is president of the council and Gordon Davis, Detroit, formerly science editor of the Cleveland *Press* and currently in charge of public relations for the Michigan Hospital Service, is the executive secretary. The council has been incorporated and has opened offices at 1402 Washington Boulevard, Detroit.

Proposed School of Industrial Health.—One of the units in the Medical Sciences Center now being developed in connection with the Wayne University College of Medicine, Detroit (THE JOURNAL, Oct. 23, 1943, p. 496), is the construction of a School of Industrial Health, it was revealed recently. While the proposed school of industrial health will confine itself to teaching and research, industrial plants will be asked to help support the program on a consultation fee basis. The school will be prepared to undertake certain research projects having to do with industry, but it will be expected that commercial firms asking for this service will finance the costs. The Medical Science Center of Wayne University is a nonprofit corporation organized under the laws of Michigan. Its object is to raise money to build and equip units of the center and to finance programs therein. The physical equipment will become the property of Wayne University, which will operate it. Full authority over curriculum, faculty appointments and program will be retained by the Wayne University administration and the board of education.

MINNESOTA

Medical Art Show.—In a news item in THE JOURNAL, July 22, page 859, describing the medical art display of the Minneapolis Public Library, the name of the late Dr. Harry B. Wilmer, Philadelphia, was used instead of that of Dr. Harry A. Wilmer, Baltimore. The names of Capt. Frank H. Netter, M. C., and Mr. Willard C. Shepard were inadvertently omitted from the names of the exhibitors.

MISSISSIPPI

Medical Women Organized.—At a recent meeting in Jackson a group of women organized and chose Dr. Virginia Small, Greenville, as president. The name selected for the new group, which is open to white women in Mississippi holding the degree of doctor of medicine, has been unofficially designated the Medical Women's Club of Mississippi. Other officers of the group include Drs. Virginia F. S. Howard, Jackson, vice president, Margaret Roe Caraway, Gulfport, secretary, and Estelle A. Magiera, Jackson, treasurer. It is planned to hold meetings during the annual session of the Mississippi State Medical Association. The new group hopes to promote a closer association of women physicians of the state socially and professionally.

MISSOURI

New Medical School Librarian.—William A. Fitzgerald, Ph.D., librarian of Brooklyn Preparatory School, Brooklyn, N. Y., has been named to a similar position at St. Louis University School of Medicine, St. Louis, newspapers report. Dr. Fitzgerald has specialized in the history of library science and taught library and social sciences in a number of schools.

Narcotic Violation.—Dr. Joseph A. McNearney, St. Louis, who was arrested at Lexington, Ky., pleaded guilty in the U. S. District Court at Lexington on June 13 to a violation of section 72, title 18, U. S. Code (forging the name of another physician to a narcotic prescription). Dr. McNearney was given a suspended sentence and placed on probation for five years, according to information from the U. S. Bureau of Narcotics.

PENNSYLVANIA

Dr. Sandy Resigns from Mental Health Bureau.—Dr. William C. Sandy, Harrisburg, since 1921 director of the mental health bureau of the Pennsylvania Department of Welfare, has resigned. Dr. Sandy was for a number of years secretary of the American Psychiatric Association.

Dr. Bull Resigns at Lehigh University.—Dr. Raymond C. Bull, organizer and director of the student health service at Lehigh University, Bethlehem, for twenty-one years, has resigned, effective July 1, because of ill health. Dr. Carl O. Keck, assistant to Dr. Bull since 1939, has been named director of the health service.

Philadelphia

Portrait of Dean Pepper.—On July 3 an oil portrait of Dr. William Pepper, dean of the University of Pennsylvania School of Medicine, was unveiled at the Free Library of Philadelphia. Dr. Pepper was president of the board of trustees of the library from 1939 to 1943.

Dr. Babcock Honored.—Dr. William Wayne Babcock, professor emeritus of surgery, Temple University School of Medicine, was recently presented with the Russell H. Conwell Award for "untiring devotion to the advancement of Temple University." The award is a large framed scroll.

Dr. Barnes Heads Biochemical Research at Sharp and Dohme.—Richard H. Barnes, Ph.D., assistant professor of physiologic chemistry, University of Minnesota, Minneapolis, has been appointed head of the department of biochemical research of Sharp and Dohme, Glenolden. He succeeds Dr. Leslie Earle Arnow, who was recently appointed director of research of the company (THE JOURNAL, June 3, p. 369).

Health Institute.—The Philadelphia County Medical Society sponsored a health institute at the board of public education, June 26-28. Included among the speakers were:

Dr. Edmund B. Spaeth, Conservation of Sight of School Children.
Dr. Carroll S. Wright, Contagious Skin Conditions Among School Children.
Dr. Frederick H. Allen, Psychiatric Services in the School System.
Dr. Waldo E. Nelson, A Tuberculosis Program in the School System.
Dr. Winthrop M. Phelps, Therapeutics of Cerebrospinal Palsy.
Lieut. Comdr. Joseph F. Hughes (MC), Electroencephalography.

Personal.—Dr. Alfred C. LaBoccett has been appointed superintendent and medical director at the Philadelphia Hospital for Contagious Diseases.——Dr. Harriet L. Hartley, chief of the division of child hygiene, department of health, was recently presented with an award of merit by the Pennsylvania Public Health Association in recognition of her services in the field of public health.——Dr. Charles A. E. Codman has been appointed honorary librarian of the Philadelphia County Medical Society.

Laboratory Named for Levi Hammond.—A laboratory of comparative anatomy in the Pfahler Hall of Science has been named the Levi J. Hammond Laboratory of Comparative Anatomy in honor of the late Dr. Levi J. Hammond. A portrait of Dr. Hammond by Susan has been hung in the main hall. It was unveiled by Mrs. Hammond. Dr. Hammond, formerly president of the Philadelphia County Medical Society, was for many years instructor in aural surgery at the University of Pennsylvania School of Medicine. He died in 1929.

Pittsburgh

George Harris Resigns as Executive Secretary.—Dr. George R. Harris, for nine years executive secretary of the Allegheny County Medical Society, retired June 20 when his term as elected secretary of the society expired. Dr. Norman C. Ochsenhirt was to succeed Dr. Harris in the elective position of secretary, but at the time of this report no one had been named to fill the post of executive secretary.

District Meeting.—The tenth and eleventh councilor districts of the Medical Society of the State of Pennsylvania held a meeting in Pittsburgh, July 20. Among the speakers were:

Dr. Francis F. Borzell, Philadelphia, Aims of the Council on Medical Service and Public Relations.
Col. Cleon J. Gentzkow, M. C., Public Health Aspects of Tropical Diseases.
Capt. William Blair Mosser (MC), Naval Surgery as of Today.
Dr. Lewis T. Buckman, Wilkes-Barre, Balanced Personality.
Dr. Augustus S. Kech, Altoona, A Challenge to Every Physician.
Dr. Paul R. Correll, Easton, The Pennsylvania Medical Practice Act.

A feature of the session was the presentation of testimonials to the following members, who have completed fifty years in the practice of medicine: Drs. William Cullen Bryant, Pittsburgh; Herbert P. Crawford, Crafton; George W. Ely, Pittsburgh; William S. Langfitt, Pittsburgh; John F. McNeely, Munhall; Jesse R. Cooper, New Castle; Charles M. Iseman, Ellwood City; John Foster, New Castle; Elizabeth M. McLaughry, New Wilmington; William A. Marsh, Mount Pleasant; Nathaniel E. Silsley, Scottdale; Charles E. Snyder, Greensburg, and Frank H. Underwood, Monongahela.

TEXAS

University Acquires Convalescent Home.—Mr. and Mrs. Maco Stewart, San Antonio and Galveston, have given their Galveston Island estate to the University of Texas Medical Branch for use as a convalescent home for children. The estate has been named the Margie B. Stewart Convalescent Home for Children. Dr. Arild E. Hansen, professor of pediatrics at the medical school, will direct the medical work at the home and Dr. George W. N. Eggers, clinical professor of orthopedic surgery, the surgical and physical therapy activities. Facilities are available for handling between 30 and 50 convalescent children, with outdoor fresh and salt water pools and special facilities for physical and occupational therapy. The project will comprise a part of the child health program of the University of Texas Medical Branch as supported by the William Buchanan Foundation of Texarkana (THE JOURNAL, February 19, p. 520).

VIRGINIA

Dr. Riggin Reappointed State Health Officer.—Dr. Irl C. Riggin, state health commissioner since 1937, has been reappointed to the office for another four year term.

Robert Hudgens Named Medical Director at Virginia Medical College.—Mr. Robert Smith Hudgens, superintendent, Emory University Hospital, Emory University, Ga., has been appointed medical director of the Medical College of Virginia, Hospital Division, Richmond, effective August 1. He succeeds Dr. Lewis E. Jarrett, who accepted a position as superintendent of Touro Infirmary, New Orleans (THE JOURNAL, May 27, p. 297).

WEST VIRGINIA

Elkins Gives Service in Tornado.—The Davis Memorial Hospital and the staff of the Golden Clinic, Elkins, gave complete services, free of charge including x-rays, medication and crutches, to victims of the recent tornado. The OCD blood bank in the hospital served all calls. It is reported that the emergency U. S. Public Health unit sent out a detachment to the Montrose area to function there. Credit is given to Col. O. I. Holeman, commandant of the West Virginia Maneuver Area, for the cooperation he gave during the catastrophe, setting up emergency stations and turning his station hospital to civilian use as necessary while corps men of the medical division assisted in the emergency.

Changes in Health Officers.—Dr. James A. Dolce, health commissioner at Wilmington, Del., has been appointed county health officer at Fairmont, succeeding Dr. Joseph W. Davis, who resigned to join the Baltimore City Health Department. ——Dr. Herbert Duncan, health officer for district number 2 at Lewisburg, has resigned to accept a residency in eye, ear, nose and throat at the Nashville General Hospital, Nashville, Tenn. Dr. Albert M. Price, Charleston, has resigned as health officer of Kanawha County to enter private practice. Dr. Price was formerly director of the state division of communicable diseases. Dr. Walter J. Riley, health officer for district number 4 at Weston, has been given an indefinite leave of absence on account of ill health.

Activities in State Health Department.—A five member advisory committee, composed of directors of various bureaus, has been set up in the state department of health by Dr. John E. Offner, Weston, state health commissioner. Members who were selected on the basis of seniority will consider personnel problems, interdivisional relationships, intradepartmental policies, legislative needs, budgeting, departmental morale and merit system qualifications. Members of the committee include J. B. Harrington, B.E., Miss Katherine E. Cox, Miss Laurene C. Fisher, R.N., Dr. Norman G. Angstadt and Dr. Charles S. McKinley. —— Miss Evelyn Yokum Fortney, vocational home economics teacher at the Shinnston High School, Harrison County, for the past five years, has been appointed nutrition consultant in the division of maternal and child hygiene of the state department of health.

GENERAL

Special Society Election.—Dr. Edward A. Schumann, Philadelphia, was chosen president of the American Gynecological Society at its meeting in Hershey, Pa., in June. Drs. Norris W. Vaux, Philadelphia, and James C. Masson, Rochester, Minn., are vice presidents, Dr. Howard C. Taylor Jr., New York, secretary, and Dr. Philip F. Williams, Philadelphia, treasurer.

Officers of Board of Pathology.—Dr. Arthur H. Sanford, Rochester, Minn., was reelected president of the American Board of Pathology at its meeting, June 7-8, in Chicago, and Drs. Frederick H. Lamb, Davenport, Iowa, and Frank W. Hartman, Detroit, were reelected vice president and secretary-treasurer, respectively. Dr. Robert A. Moore, St. Louis, was appointed assistant secretary. Drs. Howard T. Karsner, Cleveland, Alvin G. Foord, Pasadena, Calif., and Roy R. Kracke, Birmingham, Ala., have finished their two terms of service with the board and have been succeeded by Drs. Shields Warren, Boston, James B. McNaught, San Francisco, and Frederick William Sunderman, Philadelphia. Dr. Nathan Chandler Foot, New York, was elected to succeed himself.

Program on Premedical Education.—On September 14, during the annual meeting of the American Association for the Advancement of Science in Cleveland, Alpha Epsilon Delta, a national honorary premedical fraternity, will hold a special program on premedical education. Among the speakers will be Dr. Victor Johnson, Secretary, Council on Medical Education and Hospitals of the American Medical Association, Carlos I. Reed, Ph.D., professor of physiology, University of Illinois College of Medicine, and Hugh E. Setterfield, Ph.D., premedical adviser, Ohio State University, Columbus, and president of Alpha Epsilon Delta. An informal round table discussion of problems and questions from the audience will follow the talks. It is hoped that this meeting will be the beginning of similar sessions held at various national and regional meetings throughout the country.

Meeting of Obstetricians and Gynecologists.—The American Association of Obstetricians, Gynecologists and Abdominal Surgeons will hold its annual convention at the Homestead, Hot Springs, Va., September 7-9, under the presidency of Dr. Willard R. Cooke, Galveston, Texas. The preliminary program lists the following speakers:

Dr. W. Wayne Babcock, Philadelphia, An Operation for Exstrophy of the Bladder—report of 5 cases.
Dr. William S. Bainbridge, New York, Surgery of Uterine Cancer.
Dr. Bender Z. Cashman, Pittsburgh, Hysterectomy with Preservation of Ovarian Tissue in the Treatment of Endometriosis.
Dr. David P. Findley, Omaha, End Results in the Treatment of Cervicitis.
Dr. James R. Goodall, Montreal, Canada, The Defensive Mechanism of the Uterus.
Dr. Robert A. Johnston, Houston, Texas, A Critical Analysis of Twenty-Two Years' Experience with Cesarean Section.
Dr. Frederick J. Lynch, Boston, Rupture of the Pregnant Uterus.
Dr. Joe V. Meigs, Boston, The Wertheim Operation for Cancer of the Cervix.
Drs. William F. Mengert, Dallas, Texas, and Charles Rodney Stoltz, Iowa City, Total Abdominal Hysterectomy in a Series of 1,924 Patients.
Dr. James R. Miller, Hartford, Conn., Repair of Prolapse of the Urethra.
Dr. Russell J. Moe, Duluth, Minn., Duplication of Right Kidney Pelvis and Ureter with an Extravesical Opening.
Drs. Robert D. Mussey and Charles R. Maino, Rochester, Minn., Pregnancy Following Myomectomy.
Dr. James F. Norton, Jersey City, N. J., Maternal Mortality—An Analysis Based on More Than Sixty Thousand Births.
Dr. Milton G. Potter, Buffalo, Observations of Breech Deliveries in a General Hospital.
Dr. Jean P. Pratt, Detroit, Sex Precocity—Report of 4 Cases.
Dr. James K. Quigley, Rochester, N. Y., Habitual Abortion.
Dr. William A. Scott, Toronto, Canada, Surgical Complications of Pregnancy and Labor.

Dr. Cooke will deliver his presidential address on "The Differential Psychology of the American Woman." Dr. Abraham R. Abarbanel, Washington, D. C., will present "The Spasmolysant Action of Magnesium Ions on the Tetanically Contracting Human Gravid Uterus," the paper that has been awarded the annual Foundation Prize of the association.

Congress of Physical Therapy.—The American Congress of Physical Therapy will hold its twenty-third annual session at the Hotel Statler, Cleveland, September 6-9, under the presidency of Dr. Kristian G. Hansson, New York. The program will include an instruction course and, in addition, the following will speak, among others:

Dr. Miletus B. Jarman, Hot Springs, Va., Mineral Water Therapy. An Appraisal.
Drs. Louis J. Regan, Los Angeles, and John S. Hibben, Pasadena, Calif., Medical Legal Aspects of Physical Medicine.
Dr. Carl M. Peterson, Secretary, Council on Industrial Health, American Medical Association, Chicago, Industrial Rehabilitation.
Dr. Frank H. Ewerhardt, St. Louis, A Plea for a More Uniform Terminology.
Dr. Miland E. Knapp, Minneapolis, Education of the Medical Student in Physical Therapy.
Basil O'Connor, LL.D., New York, The Work of the National Foundation for Infantile Paralysis.
Dr. Donald J. Erickson, Rochester, Minn., Physical Therapy in Geriatrics.
Capt. Charles F. Behrens (MC), Activities of the Committee on Rehabilitation of the Baruch Committee.
Dr. Robert F. Dow, Battle Creek, Mich., Treatment of Military Amputees.
Dr. Arthur L. Watkins and Mary A. B. Brazier, Ph.D., Boston, Studies on Muscle Innervation.
Dr. Robert L. Bennett Jr., Warm Springs, Ga., Recognition and Treatment of Common Deformities Found in Convalescent Poliomyelitis.

The Ohio chapter of the American Physiotherapy Association will offer a special presentation Thursday: Dr. John S. Coulter, Chicago, will discuss "A Rehabilitation Center for the Injured Worker" and Catherine Graham, chief physical therapy technician, Mount Sinai Hospital, Cleveland, will give a practical demonstration in walking reeducation. Guest speakers at the annual dinner Thursday evening will be Major General George F. Lull, deputy surgeon general, Major General David N. W. Grant, air surgeon, and Rear Admiral Luther Sheldon Jr. (MC). Groups meeting during the annual congress will include the Society of Physical Therapy Physicians, September 6, and the American Registry of Physical Therapy Technicians, September 7.

LATIN AMERICA

Health Activities in Latin America. — *Shipments of Penicillin.*—Shipments of penicillin for treatment of venereal diseases in Puerto Rico have been entirely stopped, according to Dr. Ernesto Quintero, San Juan, health department specialist. The report announcing this did not give a reason for the cessation of the shipments.

San Juan Divided Into Zones for Sanitary Improvements.—Dr. Antonio Fernós-Isern, commissioner of health, plans to divide the San Juan area into eighteen zones, each zone to be supervised by a local inspector to be in charge of inspecting milk, food and drugs and check up on all sanitary regulations. The plan is a part of a program to increase the efficiency in inspecting and enforcing sanitary regulations in the metropolitan area of San Juan.

Nutrition for Crippled Children. — Crippled children of Puerto Rico are receiving special treatment and diets free through district hospitals and visiting nurse service, it was reported recently.

Society News.—The first Congress of the Mexican Faculties and Schools of Medicine was held in Monterrey City, April 2-7. Resolutions were adopted to permit local government hospitals at the disposal of the medical schools to establish a system of exchange professors at the schools and to establish requirements of the faculties to assist in their recognition as constituents of the National Federation of Medicine, according to *Medicina.*——The first National Congress of Pediatrics of Peru convened in Montevideo, July 4.——The fifth Cuban congress against tuberculosis was held in Santiago, Cuba, in May under the auspices of the National Council of Tuberculosis and the Cuban Society of Phthisiology.

Health in Puerto Rico.—In 1942 there were 32,220 deaths reported for Puerto Rico, giving a crude death rate of 16.1 per thousand of estimated population as compared with the rate of 18.6 in 1941. The 1942 rate was the lowest ever reported since the possession was admitted to the registration area in 1932. The seven principal causes of death and their death rates per hundred thousand of estimated population were diarrhea, enteritis and ulceration of the intestine 321, tuberculosis 237.3, pneumonia (all forms) and influenza 143.2, diseases of the heart 108.5, nephritis 95.9, malaria 94.9 and cancer and other malignant tumors 52. This group accounted for 65.6 per cent of all deaths. Eighty-six per cent of the deaths from diarrhea, enteritis and ulceration of the intestine were of infants and children of preschool age. A report from the U. S. Bureau of Census emphasizes the relatively large number of suicides, particularly in the age group from 15 to 24, in which 183 were recorded, giving a rate of 7. The general rate was 24.5 per hundred thousand of population. The report says that the suicide problem in Puerto Rico appears to be of about the same order of magnitude as deaths from motor vehicle accidents in the United States.

Scholarships.—Applications for scholarships to study poliomyelitis, cancer and leprosy in the United States through the Alfredo Hirsch Foundation, Buenos Aires, are now being accepted from Argentine physicians. The scholarships are awarded every two years through the Academia Nacional de Medicina of Buenos Aires, Las Heras esq. Coronel Diaz, Buenos Aires, from which additional information may be obtained.

Anniversary of Medical School.—On May 10 the Faculty of Medicine of the University of La Plata, La Plata City, Argentina, observed its twenty-fifth anniversary. The school now has about 1,476 students and graduates about 90 annually.

Personal.—Dr. Dennis F. Reeder, Panama City, has been elected president of the Panama Rotary Club for the ensuing year.——Dr. Fernando E. Tricerri, chief of the department of thoracic surgery of the Rosario University Medical School, Argentina, has gone to the United States to study surgery under a Commonwealth Fund scholarship.——Dr. Felipe F. Carranza was recently appointed a corresponding member of the Academia de Cirurgia of Rio de Janeiro.

FOREIGN

Sir John Ledingham Retires as Director of Lister Institute.—Sir John C. G. Ledingham, who retired as director of the Lister Institute of Preventive Medicine, London, has been made professor emeritus of the institute.

Memorial to Cecil Rowntree.—Plans are under way to establish a Cecil Rowntree Medical and Surgical Reference Library at the Queen Victoria Hospital, East Grinstead, in memory of Dr. Rowntree, who was honorary surgeon to the hospital for about twenty-five years. According to the *British Medical Journal,* gifts of books or funds will be appreciated to help forward the project.

Personal.—In the king's honor list recently knighthood was bestowed on Dr. Alexander Fleming, London, Howard W. Florey, Ph.D., Oxford, and Percival Hartley, D.Sc., Hampstead.——Dr. Harry L. Parker, a native of Ireland who graduated at the University of Dublin School of Physic, Trinity College, Dublin, in 1918 and who was a member of the Mayo clinic staff from 1925 to 1934, has been elected president of the Royal Academy of Medicine in Ireland and of the Dublin University Biological Association.

Medical Nobel Institute for Research. — The Royal Caroline Institute, Stockholm, in charge of the Nobel Fund for Medicine, has decided to build a Medical Nobel Institute for research in anatomy, biochemistry and physiology, according to *Science.* The institute will consist of three departments in one building to be erected on the premises of the new medical center at Norrbacka in the northwest region of the city. The Biochemical Nobel Institute was founded in 1937 and is directed by Dr. Axel Hugo T. Theorell. The physiologic department will be a Neurophysiological Research Laboratory, privately endowed in 1940 for Professor Ragnar Granit, who will also be in charge of the new institute. The anatomic department will be associated with a new chair in cell research to be founded for Dr. Torbjörn Caspersson.

Russia Provides Premium for Motherhood.—An Associated Press Dispatch from Moscow July 9 announced provisions by the supreme soviet to encourage large families ranging from up to 5,000 rubles, or $950, at birth of an eleventh child, plus a monthly payment of 300 rubles, or $57. It was reported that state aid begins with a grant of 400 rubles ($76) at birth of a third child. A fourth child brings $247 and $15.20 per month, with lump sums and monthly aid increasing thereafter. Monthly payments continue until children are 5 years old. A decree issued by the soviet also created honors for mothers, the highest one, "mother heroine," for women rearing 10 or more children, revised family taxes to encourage births, tightened laws against abortionists, liberalized aid for pregnant women and ordered increased production of baby clothes. The order of "Mother's Glory" of first, second and third class will go to women who rear 9, 8 and 7 children. The medal of motherhood first and second class will be presented to women rearing 6 and 5 children. New exemptions for pregnant women include the extension of their leave from work from 63 to 77 days, 35 before birth and 42 afterward. Mothers whose marriages are not registered will receive state relief until the children are 12 years old, and if they want to send the child or children to a state boarding school this will be done at state expense.

Foreign Letters

LONDON

(From Our Regular Correspondent)

July 8, 1944.

Pathology and the National Health Service

A group of pathologists under the chairmanship of Prof. S. P. Bedson have drawn up a statement on pathology in relation to the proposed national health service—a subject which has not received attention previously. They advocate the closest relationship between academic and applied pathology. The former, mainly concerned with teaching and research, must be centered in the medical departments of the universities, the group believes, but should not be confined to them. The efficiency of laboratories concerned chiefly with routine work can be ensured only if their staffs have an opportunity for independent investigations and benefit by the stimulus of teaching. Hence the staffing of hospital laboratories must be adequate to afford the pathologists time to make use of these opportunities as they arise. Clinical pathology is an important part of a general hospital service but is so closely related to public health bacteriology as to make division unprofitable, it is pointed out.

The university departments of pathology should retain their primary functions of teaching and research and act as training centers for pathologists to supply the needs of the service, the pathologists say. The professors should act as the friends and advisers of the pathologists in their regions and in some cases as national advisers on special subjects and research problems. The public health bacteriologic service can function as a separate administration only at its main centers and even there must be closely associated with the universities and larger hospital laboratories, if only to avoid uneconomic duplications. At the periphery there must be complete fusion. A town serving an area of 100,000 inhabitants cannot support more than one laboratory, it is held. In larger towns the hospital and public health laboratories should be under the same roof, though under separate administration. The clinical laboratories must be situated in hospitals under the disciplinary and financial, but not professional, administration of the owning authorities. Laboratory facilities must be freely at the disposal of the general practitioners in the area, but there should be no isolated, small laboratories staffed only by technicians or by a solitary pathologist. The present hospital laboratories have provided only a skeleton service for the country, the group claims, and a larger number is needed. While the professional freedom of pathologists must be maintained, some central control of the whole service of pathology will have to be exercised if it is to be conceived as one complete section of medical service to the community.

Thiouracil in the Treatment of Thyrotoxicosis

Prof. H. P. Himsworth opened a discussion on thiouracil in the treatment of thyrotoxicosis at the Royal Society of Medicine. Being much safer, thiouracil had replaced thiourea, Professor Himsworth said, though the action of the two is similar. Thiouracil does not produce the vomiting, conjunctivitis or halitosis so commonly found with thiourea, he added. Treatment is in two stages—initial and maintenance. Initial treatment is continued until there is definite regression of signs and symptoms, which takes an average of twenty-nine days, with a dosage of 0.2 Gm. five times a day. All Himsworth's cases showed considerable improvement in this stage and none became drug resistant. The first change was usually disappearance of the skin flush and the last a fall in pulse rate. The average gain in weight was 3.5 Kg. (7⅞ pounds). The basal metabolic rate fell from an average before treatment of + 39.7 to + 8.6 per cent, while the pulse rate fell from an average of 100 to 80. These improvements occurred in all cases, but other manifestations of improvement were not so consistently apparent. Exophthalmos was seldom diminished, and in most cases there was no reduction in the size of the thyroid. In other words, thiouracil controls only the manifestations of thyrotoxicosis due to the thyroid itself. It acted neither uniformly nor immediately; effects were not usually noticed until after a fortnight's treatment and the maximum effects in about four weeks. For maintenance, the smallest daily dose that would prevent remissions, usually 0.1 to 0.05 Gm., was given. Most of the patients were back at work in three months, Professor Himsworth said.

Toxic manifestations due to overdosage may appear early, when the goiter enlarges, he warned. Later they are insidious and recognizable by fatigue, depression and a bloated appearance. The toxic manifestations of idiosyncrasy are more serious and include fever, rashes, swelling of lymph glands and legs, and blood changes, of which agranulocytosis is the most serious. This proved fatal in 1 case.

A National Maternity Service

The latest manifestation of the trend toward socialization or state control of medical services is a report of the Maternity and Infant Health Services Committee of the Royal College of Obstetricians and Gynecologists, which recommends the formation of a national maternity service that would control all existing services and be controlled by a single administrative authority. Integration is regarded as absolutely essential for efficiency. It is laid down that a maternity service should have three principal aims: to bring the mother safely through pregnancy, labor and the puerperium, to secure the birth of a healthy infant and to leave the mother at the end of her confinement as well as she was when she became pregnant. In the opinion of the committee the fall in maternal mortality is by no means commensurate with the great improvements in medical science. Better use of our medical resources, the committee believes, would still further lower it. It proposes therefore that for purposes of a national service the country should be divided into areas having a population of about a million and yielding about 15,000 births a year and further divided into large "health regions."

In these regions the service would be based on key or primary centers consisting of not less than 100 lying-in beds (at least a third of them to be antepartum), antepartum and other clinics, a department for infants under a pediatrician, laboratories and teaching and research facilities. These key centers would, where possible, be part of a university medical school and have at their head a whole time professional obstetrician. In the areas the service would be based on divisional maternity centers closely associated with key centers. At the periphery would be small local centers. The whole service would act as a single unit with all parts integrated and should be actuated by the principles of continuity, completeness and cooperation.

To overcome the present difficulty, the shortage of a well trained staff, it is suggested that the university centers should be the undergraduate schools and some of the divisional centers the postgraduate schools and schools for midwives. The whole process would have to be evolved gradually until the standard of practice had been considerably raised. General practitioners should take an important share in the national service, but only those with special experience. Some improvements in postpartum treatment are urged. Hospital treatment is seldom required after childbirth, but peace and quiet and freedom from anxiety are essential. Two weeks or more in a postpartum hostel would make all the difference to the health and happiness of mother and child. Good as the work of midwives is, it would be improved by training in large maternity centers, the committee believes.

BUENOS AIRES

(From Our Regular Correspondent)

June 24, 1944.

The Argentine Quintuplets

Some months ago the daily papers announced the birth of quintuplets to a couple in Buenos Aires. The parents of the quintuplets wished to keep information on the matter private. Dr. José A. Beruti, professor of the obstetric clinic of the Faculty of Medicine of the University of Buenos Aires, who investigated the case, found that quintuplets were actually born. The grandmother had had one delivery of triplets and one of twins. A sister and sister-in-law each had two deliveries of twins. A history of twins in the father's family was not determined. Deliveries of single pregnancies during the first and second marriages were spontaneous and normal, and three children from those deliveries are normal. Five years ago the mother had an abortion of triplets at the third month of pregnancy.

During pregnancy and delivery of the quintuplets she was under the care of a midwife. The pregnancy was normal at the beginning. Edema of the legs and the abdomen and severe visual disturbances occurred from the fourth month of pregnancy on. The mother did not stop her daily work as a housewife. The midwife made a diagnosis of twins in the seventh month of pregnancy. In the course of the last month of pregnancy the mother made two excursions of twelve hours each by railroad. According to the midwife, by the end of pregnancy, which went to full term, the abdomen was large; fetal heart beats were "heard in several parts of the abdomen." The symptoms of parturition began on July 14, 1943, when the patient was transferred from her home to the midwife's house. Signs of moderate uterine contraction appeared occasionally on July 15. Subcutaneous administration of 1 cc. of posterior pituitary injection was followed by labor, which started within an hour. The infants were delivered at intervals of ten, twenty, twenty and fifty-five minutes. The bags of water ruptured spontaneously for every fetus except the third one. Delivery was spontaneous in all cases. Vertex presentation and normal delivery of normal infants occurred in 3 cases. Incomplete pelvic presentation and delivery with manual aid (delivery of the arms) occurred in 2 cases. All the infants were eupneic and cried loudly immediately after birth, except the fifth one. This last baby was born in blue asphyxia, but she was treated successfully. Every infant had the proper care and ligation of the cord before the next one was delivered. Two placentas of equal size and weight (700 Gm.) were spontaneously eliminated after delivery of the third and last infants. There were two boys and three girls. The mother had two attacks of lipothyma after delivery of the first and last babies and hypotonia of the uterus before delivering the last baby. A second subcutaneous administration of posterior pituitary injection was done before delivery of the fifth baby. Five hundred cc. of isotonic solution of sodium chloride, injections of proper doses of ergotine and caffeine and stimulants were administered to the mother after parturition. She was put in the Trendelenburg position with an ice bag on the abdomen (uterus). Total duration of delivery was nineteen hours and twenty-five minutes. The amount of eliminated amniotic fluid was about 500 cc. The amount of blood lost was about 1,000 cc. The weight of the infants twenty-four hours after birth was, in order of delivery, 1,300, 1,200, 1,150, 1,500 and 1,250 Gm. (300 Gm. more for the whole group than for the Dionne sisters). The mother never permitted the midwife to call a physician. The puerperium was normal.

The children were not premature. They showed great vitality. On the second day they began to have a mixture of colostrum from the mother, cow's milk and water. The infants were not put in incubators. Oxygen and carbon dioxide were not administered. The infants were not put in a bath for the first three months of life. The weight of the infants at the age of 8 months and 10 days was 8,800, 8,800, 7,500, 8,400 and 7,500 Gm. They are healthy and beginning to cut teeth.

Interrelation of Hypophysis and Adrenal Glands Demonstrated by Parabiosis

Drs. B. A. Houssay and R. M. Pinto recently read papers before the members of the Sociedad Argentina de Biologia. They said that there is a functional correlation between the anterior part of the hypophysis and the adrenal glands. The former forms and eliminates adrenotropin, which stimulates the cortical functions of the latter and the production of which is regulated by certain substances produced by the adrenal cortex. Removal of the adrenal glands results in an increased production of adrenotropin. The union in parabiosis of a normal rat to another rat which has previously been deprived of the adrenal glands results in the production of adrenal hypertrophy of the normal rat, which hypertrophy is more pronounced if the parabiosic adrenalectomized rat is castrated before adrenalectomy. Sex glands and thyroids have no role in the production of adrenal hypertrophy of parabiotic rats, which is accompanied by increased secretion of hormones which produce atrophy of the thymus. The administration of large doses of desoxicorticosterone to adrenalectomized rats results in regeneration of the adrenal glands, with consequent diminution of the secretion of adrenotropin.

Use of Fish in Antimalarial Crusade

Dr. Alfredo Correas was appointed some time ago by the General Department of Malaria, which is a branch of the Argentine Department of Public Health and Social Assistance, to carry on studies which aimed to find out whether or not autochthonous fishes of the northern section of Argentina are larviphagic. Dr. Correas recently gave his report on the subject. He said that the larviphagic properties of autochthonous fishes of that section of the country are so mild that the fishes are of no value in the antimalarial program. He recommended the transplantation and breeding of voracious laviphagic species, such as gambusia fishes (schizophallus) of the southeastern section of the United States; the colisa, macropodus, trichogaster and beta species of the southeastern part of Asia, South Africa, the Nile River and the Congo; and also Debistes reticulatus Peters of South America.

Marriages

JOHN JUNIOR THOMPSON, Winona, Minn., to Miss Jewell Stanford of Willard, N. C., in Winston-Salem, N. C., June 24.

JAMES W. REAGAN, Warren, Ohio, to Lieut. Angelyn B. Boezeman of De Motte, Ind., in Fort Custer, Mich., June 1.

WESLEY HARVEY STONEBURNER, Wooster, Ohio, to Miss Mary Elizabeth Banks of Winchester, Tenn., July 3.

ANTHONY F. CARAVELLI, Haddon Heights, N. J., to Miss Olga F. Grellner of University City, Mo., June 29.

LOUIS FABIEN PINE, Burlington, Vt., to Miss Anita Evelyn Du Guay of Worcester, Mass., June 24.

ARTHUR J. HEWETT, Newbury, Mass., to Miss Mary Elizabeth Hogan of West Newbury, June 28.

HALLOWELL DAVIS, Boston, to Miss Florence Eaton of New York in Waterville, Maine, June 29.

JAMES J. MATEJKA JR., Chicago, to Miss Marie Agnes Murphy of Beloit, Wis., June 3.

HARLOW F. BANFIELD, Wellsville, Ohio, to Miss Geneva McCaulla of Springfield, July 8.

FORREST R. MARTIN, Paris, Ill., to Mrs. Cauline McKinney Staley of Decatur, June 20.

WILLIAM HENRY SHULL to Miss Cecelia Day Nuchols, both of Charlotte, N. C., June 1.

Deaths

Robert Morton Smith ✠ West Warwick, R. I.; College of Physicians and Surgeons, Baltimore, 1889; formerly member and president of the state board of health; instrumental in organizing the Kent County Medical Society, serving as its first president; one of the founders of the Pawtuxet Valley Visiting Nurse and Anti-Tuberculosis Association in 1908 and served continuously as chairman of the tuberculosis committee of the association; during World War I an examiner for the local draft board and chairman of the disaster relief unit of Pawtuxet Valley Branch of Providence Chapter, American Red Cross; formerly medical examiner for the State Sanatorium at Wallum Lake; member of the Pawtuxet Valley Chamber of Commerce, Rhode Island Historical Society, National Geographic Society and the Museum of Natural History; died July 10, aged 80, of general arteriosclerosis and cerebral thrombosis.

Clarence James McMullen, Los Angeles; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1912; member of the Illinois State Medical Society; fellow of the American College of Physicians; specialist certified by the American Board of Internal Medicine; served as assistant professor of medicine at Northwestern University Medical School, Chicago, as professor of internal medicine at the Illinois Post-Graduate Medical School and as assistant clinical professor of medicine at Rush Medical College, Chicago; formerly attending physician, Cook County Hospital and the Washington Boulevard hospitals, Chicago, and the City of Chicago Municipal Tuberculosis Sanitarium; died May 24, aged 54, of hypertensive heart disease.

William Edward Nesbit ✠ San Antonio, Texas; Johns Hopkins University School of Medicine, Baltimore, 1913; Army Medical School, 1918; fellow of the American College of Physicians; specialist certified by the American Board of Internal Medicine; chairman of the Procurement and Assignment advisory committee for Bexar County during World War II; served as chairman of the Selective Service System at San Antonio for two years and as civilian examiner at Induction Center, Camp Dodd, since its inception; served during World War I; a charter member of the Texas Club of Internists, of which he had been one of the organizers and past president; on the staffs of the Nix and Santa Rosa hospitals; died April 5, aged 55, of encephalitis.

Joseph Boardman Noble, Waukesha, Wis.; Rush Medical College, Chicago, 1886; member of the State Medical Society of Wisconsin; past president of the Waukesha County Medical Society; at one time owner of a hospital in Tower, Minn.; appointed city physician of Waukesha in 1902; for many years medical examiner for the New York, Mutual, Penn and Northwestern Life Insurance companies; formerly member of the library board and alderman; served as physician for the Wisconsin Industrial School for Boys; for twenty-five years surgeon for the Northwestern Railway; on the staff of the Waukesha Memorial Hospital, where he died May 7, aged 85, of cerebral arteriosclerosis.

Reeve Beecher Howland ✠ Elmira, N. Y.; New York Homeopathic Medical College and Hospital, New York, 1895; past president of the Chemung County Medical Society; in 1897 joined the New York National Guard and served as assistant surgeon with the third New York Volunteer Infantry, assigned to duty in Virginia, during the Spanish-American War; later battalion surgeon and assistant regimental surgeon with the rank of captain; served as medical examiner for the U. S. Army recruiting office; for many years health officer of Elmira; on the staffs of the Arnot-Ogden Memorial and St. Joseph's hospitals; died in New York May 12, aged 74, of coronary thrombosis.

Farrar Cobb, Hyannis, Mass.; Harvard Medical School, Boston, 1893; member of the Massachusetts Medical Society and the New England Surgical Society; fellow of the American College of Surgeons; at one time lecturer on surgery at his alma mater; served on the staff of the Massachusetts General Hospital and as superintendent of the Massachusetts Eye and Ear Infirmary in Boston; chief surgeon from 1930 to 1935 and on the consulting staff from 1930 to 1944 of the Cape Cod Hospital, where he died May 30, aged 77, of cerebral and general arteriosclerosis and uremia.

John Bunyan Acken, Griggstown, N. J.; University of the City of New York Medical Department, New York, 1885; formerly on the staffs of the Blackwell's Island Hospital, the Northwestern Dispensary and Bellevue Hospital in New York; died May 16, aged 88, of chronic myocarditis and arteriosclerosis.

Clifford William Andrews, Waupaca, Wis.; Bennett Medical College, Chicago, 1911; at one time health officer of Beloit; served during World War I; major, medical reserve corps of the U. S. Army, not on active duty; on the staff of the City Hospital; died May 4, aged 62, of coronary thrombosis.

Jabez Eldridge Armstrong ✠ Greenwich, N. Y.; University of Buffalo School of Medicine, 1904; for many years health officer of the town of Greenwich; member of the associate staff of the Mary McClellan Hospital, Cambridge; died June 3, aged 74, of arteriosclerosis and coronary disease.

Charles Harper Baker, Bay City, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1882; member and in 1919 president of the Michigan State Medical Society; life member and past president of the Bay County Medical Society; member of the American Academy of Ophthalmology and Otolaryngology; on the staffs of the Mercy and General hospitals; died July 7, aged 84, of carcinoma of the stomach.

George Edward Baldwin ✠ Green Lake, Wis.; University of the City of New York Medical Department, New York, 1890; an Affiliate Fellow of the American Medical Association; died May 10, aged 78, of coronary thrombosis, cardiorenal disease and hypertension.

John Henry Becker Jr., Port Jefferson Station, N. Y.; Long Island College Hospital, Brooklyn, 1907; died April 25 of cerebral hemorrhage, hypertension and arteriosclerosis.

Pierre Bergeron, Manchester, N. H.; Laval University Faculty of Medicine, Quebec, Que., Canada, 1904; member of the New Hampshire Medical Society; served during World War I; died May 7, aged 62, of chronic myocarditis, myocardial decompensation and coronary thrombosis.

Thackery Louis Berry, Frankfort, Ky.; Meharry Medical College, Nashville, Tenn., 1915; died June 7, aged 54.

Walter Day Biggs, Lometa, Texas (licensed in Texas by years of practice); health officer; died May 11, aged 71, of carcinoma of the throat.

Harry Bock, Ossining, N. Y.; Bellevue Hospital Medical College, New York, 1898; died April 10 of generalized arteriosclerosis.

John C. Boyle, Medical Lake, Wash.; Wisconsin College of Physicians and Surgeons, Milwaukee, 1903; assistant superintendent and later assistant physician of the Eastern State Hospital; died May 7, aged 66.

Charles Edward Brain, Salt Lake City; Jefferson Medical College of Philadelphia, 1910; member of the Utah State Medical Association; served during World War I; member of the senior staff, St. Mark's Hospital; died June 4, aged 57, of coronary occlusion due to coronary sclerosis.

Jennie Nicholson Browne, Baltimore; Woman's Medical College of Baltimore, 1902; formerly professor of physiology at her alma mater; died June 21, aged 68, of coronary occlusion, chronic myocarditis and arteriosclerosis.

John Harold Buffum ✠ Wallingford, Conn.; University of Vermont College of Medicine, Burlington, 1898; died in the Meriden Hospital, Meriden, May 28, aged 69, of pneumonia.

Ervin M. Campbell, Ferriday, La.; Memphis (Tenn.) Hospital Medical College, 1906; served as coroner; died May 16, aged 68, of myocarditis.

Quinn C. Cantrell, McMinnville, Tenn.; University of Tennessee Medical Department, Nashville, 1908; for many years health officer of Warren County; died June 7, aged 64, of cerebral hemorrhage.

Benjamin Franklin Chambers, Port Arthur, Texas; Memphis (Tenn.) Hospital Medical College, 1901; member of the State Medical Association of Texas; on the staff of St. Mary's Hospital, Gates Memorial; died May 18, aged 70, of myeloma.

William Levi Clark, Hoosick, N. Y.; University of Vermont College of Medicine, Burlington, 1885; member of the Medical Society of the State of New York; served in the medical corps of the U. S. Army during World War I; served as health officer of Hoosick; died in a hospital at Albany June 16, aged 80.

Marsden Treutlen Cleckley, Augusta, Ga.; Hahnemann Medical College and Hospital of Philadelphia, 1895; died May 8, aged 73.

Edward Moody Cook ✠ York Harbor, Me.; Harvard Medical School, Boston, 1924; diplomate of the National Board of Medical Examiners; served overseas during World War I; died in May, aged 44, of periarteritis nodosa.

Orris Graem Cruikshank, Terre Haute, Ind.; Central College of Physicians and Surgeons, Indianapolis, 1898; surgeon for the Chicago, Milwaukee and St. Paul Railroad; died June 17, aged 83, of cerebral hemorrhage.

George Washington Gutler, Prescott, Ariz.; Harvard Medical School, Boston, 1892; died June 3, aged 78.

Homer J. Davidson ✠ Seattle; Johns Hopkins University School of Medicine, Baltimore, 1905; fellow of the American College of Surgeons; on the staffs of the Swedish Hospital and the Columbus Hospital, where he died May 28, aged 66, of uremia.

Lafayette Millard Davis, Roanoke, Va.; Kentucky School of Medicine, Louisville, 1904; medical examiner for the Norfolk and Western Railway Company; died May 6, aged 62.

Harry W. Dechert, Orwigsburg, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1895; member of the Medical Society of the State of Pennsylvania; served on the staff of the Pottsville Hospital, Pottsville; for many years examining physician for the Reading Railroad; died in the Schuylkill County Hospital, Schuylkill Haven, May 29, aged 71, of diabetes mellitus, arthritis and disease of the prostate.

Robert W. Dixon, Dixon, Ky.; Kentucky School of Medicine, Louisville, 1896; died May 29, aged 74.

Michael Joseph Dowd ✠ Thompsonville, Conn.; Baltimore Medical College, 1901; examiner for the Metropolitan Life Insurance Company for many years; served as examiner for the Connecticut State Boxing Commission; on the staff of the Mercy Hospital, Springfield, Mass., where he died April 4, aged 75, of prostatitis and acute cardiac failure.

Sylvester A. J. Ennis ✠ Shullsburg, Wis.; Milwaukee Medical College, 1910; president of the LaFayette County Medical Society; served during World War I; owner of Dr. Ennis' Hospital; organizer of the LaFayette County Tuberculosis Clinic at Darlington; surgeon for the Chicago, Milwaukee and St. Paul Railway; president of the Shullsburg Park Commission since the park was established; died in the Wisconsin General Hospital, Madison, May 19, aged 58, of arteriosclerotic heart disease.

Samuel Clyde Fittz, Winnfield, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1907; member of the Louisiana State Medical Society; served as parish coroner; medical examiner for Winn Parish Selective Service Board during World War I and II; senior member of the Fittz-Faith Clinic; died May 14, aged 63.

Maurice Monroe Fleagle, Hanover, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1896; past president of the board of health; on the staff of the Hanover General Hospital; died May 30, aged 72, of coronary thrombosis.

Andrew H. Frankel, Chicago; Wisconsin College of Physicians and Surgeons, Milwaukee, 1906; senior lieutenant in the U. S. Naval Reserve during World War I, serving later with the same rank in the regular navy; on the staffs of the American and John B. Murphy hospitals; died May 29, aged 61, of cerebral hemorrhage, arteriosclerosis and chronic nephritis.

Robert Lionel Gordon, Woodside, La.; Tulane University of Louisiana School of Medicine, New Orleans, 1922; member of the Louisiana State Medical Society and the American Urological Association; served an internship at the U. S. Marine Hospital number 14 in New Orleans; on the staffs of Hotel Dieu, Mercy, Baptist and French hospitals, New Orleans, serving at one time as president of the staff of the last; died May 5, aged 44, of diabetes mellitus and coronary thrombosis.

Middleton Howard Hagood ✠ Brewton, Ala.; Medical College of Alabama, Mobile, 1898; for many years secretary of the Escambia County Medical Society; served in France during World War I; member of the board of education; died in a hospital at Montgomery May 21, aged 70, of coronary occlusion.

Charles Huse Hale, Boswell, Okla.; Kentucky School of Medicine, Louisville, 1908; member of the Oklahoma State Medical Association; served as president of the Choctaw County Medical Society; examiner for the Frisco Railroad; died April 25, aged 70, of heart disease.

Frederick A. Hayes, Buffalo; Niagara University Medical Department, Buffalo, 1892; member of the Medical Society of the State of New York; died April 30, aged 78, of coronary sclerosis and arteriosclerotic heart disease.

Arthur Hebb, Baltimore; Baltimore Medical College, 1898; member of the Medical and Chirurgical Faculty of Maryland; served on the staff of the Johns Hopkins Hospital; died April 24, aged 66, of hypostatic pneumonia, cerebral thrombosis, general arteriosclerosis and diabetes mellitus.

James Burch Joyce, Baltimore; University of Maryland School of Medicine, Baltimore, 1894; formerly member of the city health department; died May 21, aged 72, of subarachnoid hemorrhage and hypertensive cardiovascular disease.

Benjamin Edward Kaplan, Newark, N. J.; University and Bellevue Hospital Medical College, New York, 1905; died May 21, aged 60, of coronary thrombosis and arteriosclerotic heart disease.

Andrew Edward Kepert, Calumet City, Ill.; Jenner Medical College, Chicago, 1905; also a pharmacist; died in St. Margaret Hospital, Hammond, Ind., May 26, aged 65, of carcinoma of the liver.

John Jay Kinney, Wooster, Ohio; University of Wooster Medical Department, Cleveland, 1889; member of the Ohio State Medical Association; on the staff of the Community Hospital, formerly known as the Kinney Hospital, of which he had been the founder, and physician in charge of the Kinney-Knestrick Hospital and the Kinney Memorial Emergency Hospital; died in the Flagler Hospital, St. Augustine, Fla., May 14, aged 79, of coronary thrombosis.

Harry Wadsworth Long ✠ Escanaba, Mich.; Northwestern University Medical School, Chicago, 1900; served during World War I; on the staff of St. Francis Hospital; died May 30, aged 65, of coronary thrombosis.

William J. McKown, Albany, N. Y.; Albany Medical College, 1894; member of the Medical Society of the State of New York; a captain in the New York National Guard from 1905 to 1911; on the staff of the Memorial Hospital; died May 28, aged 72, of carcinoma of the throat.

Orville Bruce Moon ✠ Bisbee, Ariz.; Vanderbilt University School of Medicine, Nashville, Tenn., 1915; city and county health officer; for many years a member of the staff of the Copper Queen Hospital; member and past president of the Kiwanis Club; died in Warren May 22, aged 54, of coronary thrombosis.

Charles Arthur Mooney, Ferndale, Mich.; University of Michigan Medical School, Ann Arbor, 1916; member of the Michigan State Medical Society; first lieutenant in the medical corps of the U. S. Army during World War I; health officer of Ferndale; a member of the board of trustees of the Oakland County Tuberculosis Sanatorium, Pontiac, from 1938 to 1940, when he became chairman of the board; on the staff of the Mount Carmel Mercy Hospital, Detroit, where he died May 30, aged 54, of pneumonia and heart disease.

Joseph Sauter Muller, New Orleans; Medical Department of Tulane University of Louisiana, New Orleans, 1905; member of the Louisiana State Medical Society; served with the U. S. Immigration Service during World War I; died in the Hotel Dieu, Sisters' Hospital May 19, aged 60, of acute myocarditis.

Frank Edward Murphy, St. Louis; St. Louis University School of Medicine, 1920; died in the Missouri Baptist Hospital May 18, aged 51, of lobar pneumonia.

John H. Neary, Detroit; Michigan College of Medicine and Surgery, Detroit, 1900; member of the Michigan State Medical Society; active in the founding and on the staff of St. Joseph's Mercy Hospital, where he died May 21, aged 68, of cardiac failure and carcinoma of the sigmoid.

Martin Landis Nissley ✠ Hummelstown, Pa.; Medico-Chirurgical College of Philadelphia, 1905; for many years member and president of the school board; served as director and president of the Hummelstown National Bank; president of the Hummelstown Mutual Fire Insurance Company; physician for the Paxtang draft board during World War I; medical superintendent of the Dauphin County Hospital, Harrisburg; died May 26, aged 62, of heart disease.

James Albert Northcross, Chicago; Meharry Medical College, Nashville, Tenn., 1919; found drowned May 27, aged 54.

John Hanly O'Connell ✠ Topeka, Kan.; St. Louis University School of Medicine, 1909; treasurer and past president of the Kansas Medical Society; served during World War I; on the staffs of Christ's Hospital, St. Francis Hospital and the Stormont Hospital, where he died May 22, aged 59, of coronary thrombosis and arteriosclerosis.

Carolyn L. Olendorf ✠ Cobleskill, N. Y.; Woman's Medical College of Pennsylvania, Philadelphia, 1899; died May 28, aged 69, of cerebral hemorrhage.

Walter Peter **Prudhomme,** Pineville, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1906; member of the Louisiana State Medical Society; served overseas during World War I; served on the staff of the Central Louisiana State Hospital; died April 4, aged 62.

Bert E. **Purcell** ✠ Iowa Falls, Iowa; State University of Iowa College of Medicine, Iowa City, 1898; member of the city council; died May 15, aged 70, of coronary occlusion.

John **Willard Robinson,** Grand Rivers, Ky.; Kentucky School of Medicine, Louisville, 1897; member of the Kentucky State Medical Association; died June 1, aged 78, of cirrhosis of the liver.

Samuel **Theodore Roeder Jr.,** Baltimore; University of Maryland School of Medicine, Baltimore, 1891; died April 26, aged 75, of chronic myocarditis, nephritis and arteriosclerosis.

Rupert **Reed Rogers,** Warren, Ohio; Columbia University College of Physicians and Surgeons, New York, 1914; member of the Ohio State Medical Association and the American Academy of Pediatrics; a member of the staff of the Warren City Hospital; died April 20, aged 56, of multiple myeloma.

William **Frederick Saybolt,** Forest Hills, N. Y.; University of Pennsylvania Department of Medicine, Philadelphia, 1902; member of the Medical Society of the state of New York; fellow of the American College of Surgeons; served on the staffs of the Mary Immaculate Hospital, Jamaica, St. Catherine's and the Lutheran hospitals, Brooklyn, and the Doctors Hospital, New York; died in St. Francis Hospital, Port Jervis, June 20, aged 65.

Charles **Edward Schoff** ✠ Sacramento, Calif.; Cooper Medical College, San Francisco, 1908; specialist certified by the American Board of Dermatology and Syphilology; member of the state board of medical examiners from 1929 to 1940; served on the staffs of the Sacramento County and Sutter General hospitals; died May 28, aged 59, of cerebral embolism.

Winthrop **Davis Scudder,** West Hartford, Conn.; Harvard Medical School, Boston, 1920; member of the Connecticut State Medical Society; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; on the staff of the Hartford Hospital, Hartford; died in the New England Deaconess Hospital, Boston, May 13, aged 50, of glioblastoma multiforme of one cerebral hemisphere.

Edwin **J. Siegmund,** Wabash, Ind.; Chicago Homeopathic Medical College, 1901; served as health officer of Wabash County and as school doctor; died May 25, aged 68, of heart disease.

Albert **French Storke,** Oak Park, Ill.; the Hahnemann Medical College and Hospital, Chicago, 1890; member of the Illinois State Medical Society; formerly health officer of Oak Park and secretary of the department of health; died in the West Suburban Hospital May 28, aged 75, of chronic myocarditis and cerebral embolism.

Clifford **William Walden,** Beatrice, Neb.; John A. Creighton Medical College, Omaha, 1896; died in the Bishop Clarkson Memorial Hospital, Omaha, May 11, aged 67, of pneumonia.

Silas **Anderson Walker,** La Follette, Tenn.; Tennessee Medical College, Knoxville, 1894; died in a Knoxville hospital May 21, aged 79, of cerebral hemorrhage.

Samuel **Arthur Watts,** Marlin, Texas; Medical Department of Grant University, Chattanooga, Tenn., 1902; member of the State Medical Association of Texas; urologist, Torbett Clinic and Hospital; died April 21, aged 69, of chronic bronchitis and acute pneumonia.

Karl **Robert Werndorff,** Council Bluffs, Iowa; Medizinische Fakultät der Universität Wien, Austria, 1902; member of the Iowa State Medical Society, Clinical Orthopedic Society and the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; on the staff of the Jennie Edmundson Memorial Hospital; died May 28, aged 66, of coronary thrombosis.

Lyle **Livingstone Wyse,** Hamburg, N. Y.; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1931; member of the Medical Society of the State of New York; interned at the Toronto General Hospital and the Hospital for Sick Children in Toronto; served as resident in otology, laryngology and rhinology at the Buffalo General Hospital; on the staffs of Our Lady of Victory Hospital in Lackawanna, Buffalo General, Children's and Mercy hospitals in Buffalo; died May 21, aged 38, of coronary occlusion.

DIED WHILE IN MILITARY SERVICE

Frederick Henry Dieterich ✠ Miami, Fla.; Columbia University College of Physicians and Surgeons, New York, 1910; specialist certified by the American Board of Pathology, Inc.; formerly on duty at the Peking Union Medical College, Peking, China; served as an instructor in surgery at his alma mater, director of pathology at the Creighton University Medical School, Omaha, and later served at the Rockefeller Institute in New York; formerly professor of pathology at the Medical College of the State of South Carolina, Charleston, where he had been consultant pathologist at the State Hospital; formerly director of laboratories at the Good Samaritan Hospital, Cincinnati, and on the staffs of the James M. Jackson Memorial Hospital, Miami, and St. Francis Hospital, Miami Beach; formerly pathologist for the department of welfare in New York City and director of bureau of laboratories, department of public health at Yonkers, N. Y.; served during World War I; commissioned a major in the medical corps, Army of the United States, on April 28, 1942; U. S. Army laboratory officer at the AAF Regional Station Hospital, Barksdale Field, La., where he died February 16, aged 56, of coronary occlusion.

Roland Nickolaus Klemmer ✠ Lancaster, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1922; diplomate of the National Board of Medical Examiners; specialist certified by the American Board of Internal Medicine; member of the American Heart Association; fellow of the American College of Physicians; served as chief of the medical staff, Lancaster General Hospital; commissioned a lieutenant commander in the medical corps of the U. S. Naval Reserve on Aug. 11, 1941 and began active duty on Dec. 29, 1941; later promoted to commander; died aboard ship in the Pacific area May 9, aged 46, of chronic myocarditis.

Leo Hartney McMahon ✠ Breckenridge, Minn.; St. Louis University School of Medicine, 1925; served on the staff of St. Francis Hospital; commissioned a lieutenant commander in the medical corps of the U. S. Naval Reserve on Nov. 18, 1943; a medical officer at the Great Lakes Naval Training Center, Great Lakes, Ill.; died in Waukegan, Ill., May 29, aged 42.

Ross Mayberry Newman ✠ Kansas City, Mo.; Washington University School of Medicine, St. Louis, 1931; specialist certified by the American Board of Urology, Inc.; member of the American Urological Association; fellow of the American College of Surgeons; assistant in surgery at the University of Kansas School of Medicine, Kansas City, Kan.; attending surgeon in urology at the Kansas City General Hospital; chairman of the department of urology, St. Joseph Hospital; member of the executive staff in urology at the Research Hospital; member of the visiting staff in urology at St. Luke's Hospital and St. Mary's Hospital; on May 22, 1942 commissioned a captain in the medical corps, Army of the United States, beginning extended active duty on May 31, 1942; later promoted to major; died in Chicago June 10, aged 38.

John Joseph Whoriskey Jr., Cambridge, Mass.; Tufts College Medical School, Boston, 1942; diplomate of the National Board of Medical Examiners; served an internship at the Newton Hospital, Newton; first lieutenant, medical corps, Army of the United States; died on board ship en route to the American area April 13, aged 26.

Robert James Wilson ✠ Lieutenant Colonel, M. C., U. S. Army, Buffalo; University of Buffalo School of Medicine, 1931; Army Medical School, 1933; commissioned a first lieutenant in the medical reserve corps of the U. S. Army in 1931; entered the medical corps of the U. S. Army in 1932; promoted to captain in 1934, major on July 1, 1943 and later to lieutenant colonel; interned at the Walter Reed General Hospital, Washington, D. C., where he served as assistant chief ward officer in the surgical service; later assigned to the Army and Navy General Hospital at Hot Springs National Park, Ark.; in 1941 became associated with the Office of the Surgeon General Finance and Supply Division; later chief of the Civilian Personnel Division; staff officer of the U. S. Army Bruns General Hospital, Sante Fe, N. M., where he died July 14, aged 38.

Bureau of Investigation

STIPULATIONS

Agreements Between Federal Trade Commission and Promoters of Various Products

Following are abstracts of stipulations in which promoters of "patent medicines," medical devices and cosmetics have agreed, following action by the Federal Trade Commission, to discontinue certain misrepresentations in their advertising. These stipulations differ from the "Cease and Desist Orders" of the Commission in that such orders definitely direct the discontinuance of misrepresentations. The abstracts that follow are presented primarily to illustrate the effects of the provisions of the Wheeler-Lea Amendment to the Federal Trade Commission Act on the promotion of such products:

Black-Draught, Syrup of Black-Draught and Black Draught (Granulated).—That these preparations contain a tonic, help to tone lazy intestinal muscles or the digestive system, or have any effect on a sallow complexion were misrepresentations which the Chattanooga Medicine Company and Nelson Chesman Company, an advertising agency, both of Chattanooga, Tenn., agreed to eliminate from the advertising, in a stipulation that they entered into with the Federal Trade Commission in August 1943. They agreed, further, not to publish any advertisement which fails to reveal that these products should not be used when abdominal pain, nausea, vomiting or other symptoms of appendicitis are present, provided, however, that such advertisement need only contain the statement, "Caution: Use only as directed" if the label instructions for use bear a warning to the same effect.

Crysta-Jell and Reducers Skin Lotion.—These are put out by Eugene Schiff, trading as Schiff Bio-Food Products, Detroit. In September 1943 he entered into a stipulation with the Federal Trade Commission in which he agreed to discontinue the following advertising misrepresentations: That Crysta-Jell will restore energy or health, preserve health, youth or appearance, cure obesity, satisfy hunger, or effect a loss of 3 to 4 pounds of weight per week or in any other definitely stated amount within any given period of time; that it contains no drugs or chemicals, that it is a vegetable gelatin compound or a vegetable compound, or that Reducers Skin Lotion will keep the skin firm.

Hanovia Alpine Sun Lamp.—The Hanovia Chemical & Manufacturing Company, Newark, N. J., entered into a stipulation with the Federal Trade Commission in September 1943 in which it agreed to discontinue the following misrepresentations in the sale of this device: That the rays from the lamp are equivalent to those of the sun in physical or therapeutic properties, and that through its use a person may enjoy all the health-giving benefits of sunshine; that because of its quartz burner the lamp possesses all the healing and tonic qualities of ultraviolet lamps; that the use of the lamp will clear the complexion of blemishes, build resistance against colds and disease, assure sound teeth, stabilize the nerves, kill bacteria, shorten a period of convalescence, and be an indispensable means to beauty, and that it is endorsed by the medical profession the world over for unsupervised home treatment. The concern further stipulated that it would discontinue any advertisement or trade literature which failed to reveal clearly that exposure to the lamp with respect to either proximity or length of time may result in injury to the user; that the device should not be used in cases of pellagra, lupus erythematosus, or certain types of eczema, and that it should never be used unless goggles are worn to protect the eyes. The stipulation provided, however, that such advertising need contain only the statement, "Caution: Use only as directed" when the directions on the label include a warning to the same effect.

Histeen Tablets.—On Aug. 23, 1943, the Histex Corporation, Chicago, entered into a stipulation with the Federal Trade Commission, agreeing to discontinue any advertisement which did not reveal that Histeen Tablets should not be taken by persons having heart or kidney ailments, except on competent medical advice, and that the product may cause serious blood disturbances if taken frequently or continuously. It was provided, however, that such advertisements need contain only the statement, "Caution: Use only as directed" if the directions for use contain a warning to the same effect. This preparation is sold as a hay fever treatment, and an earlier stipulation was entered into in February 1938 by the promoters, in which they agreed to discontinue representing that Histeen will give relief for hay fever sufferers in a radically different way, that it works like magic and eliminates every trace of hay fever suffering for an entire season; that it is the fastest acting cold remedy and will relieve "other miseries" unless this latter claim is qualified so as to show the therapeutic limitations of the product.

Mistol Drops and Mistol Drops with Ephedrine.—In September 1943 Stanco Incorporated, New York, which puts out these products, and McCann-Erickson, Inc., which handles the advertising, stipulated with the Federal Trade Commission to discontinue any advertisements which failed to reveal that these preparations should not be administered to undernourished infants, abnormally weak children or debilitated elderly persons; that frequent or excessive use of Mistol Drops should be avoided and that such use in the case of the other Mistol product might cause nervousness, restlessness or sleeplessness, and that persons suffering from high blood pressure, heart disease, diabetes or thyroid trouble should not use the ephedrine product except on competent advice. The stipulation provided, however, that such advertising need contain only the statement, "Caution: Use only as directed" if and when the directions for use are given on the label and carry a warning to the same effect.

Pomade Gonzalez.—This is put out by one Espiridion Gonzalez, Laredo, Texas, who stipulated with the Federal Trade Commission in August 1943 that he would cease representing that the product may give excellent results in cases of ringworm, warts or skin sores, or will remove all kinds of skin eruptions. He further agreed to discontinue any advertisements which failed to reveal that the Pomade contains 50 per cent of salicylic acid and that a product of this strength, when repeatedly applied to the skin (other than two or three applications for hard corns and calluses) will cause local irritation. It was provided, however, that such advertisements need only contain the statement, "Caution: Use only as directed" if the label directions bear a warning to the same effect.

Posture-Aid.—This alleged health device is put out by J. W. Cole, trading as Posture-Aid Company, Dallas, Texas. In August 1943 Cole, with John and Evelyn Brough, who conduct the agency handling the Posture-Aid advertising, stipulated with the Federal Trade Commission that they would discontinue the following advertising misrepresentations: That the device relieves constipation, headache, backache, nervousness, fatigue or tenseness; pulls muscles into place, relaxes or strengthens them, relieves tired or cramped muscles or trains them to hold the body erect; corrects misplaced vertebrae, double chin, round shoulders, swayback or flat chest, lifts the chest or gives greater room for lung expansion, flattens the stomach, promotes health, appetite, well-being, new energy, beauty of figure or improved posture, exercises the muscles of the neck or tones, relaxes, straightens or stretches the spine.

S. P. S. Scalp Food.—In August 1943 Samuel P. Shokunbi, trading as the S. P. S. Chemical Company, Chicago, entered into a stipulation with the Federal Trade Commission in which he agreed to discontinue the following advertising misrepresentations: That the product will feed or nourish the scalp, promote the growth or improve the grade of hair, or be a cure or remedy for itching scalp, eczema, conditions which cause falling hair or dandruff, except in so far as its use will facilitate the mechanical removal of loose scales of dandruff. The respondent further agreed to cease representing, through the use of the term "Scalp Food" or any other expression of similar meaning, that the product will feed or nourish the scalp.

Vita-Fluff, Lovili and Glamour.—These are put out by Donald H. and Matilda Miller, trading as Northern Research Industries, Dayton, Ohio. In a stipulation which they entered into with the Federal Trade Commission in August 1943, they agreed to discontinue the following advertising misrepresentations: That Vita-Fluff adds natural sheen or any sheen or luster to the hair; that Lovili is not similar to Vita-Fluff, and that the two are not identical, except for a small content of synthetic oil added to Lovili; that Lovili creates a true sheen which will last indefinitely or for any longer time than that produced by ordinary oil shampoos; that Glamour is made from actual lemon, or that, as an acid-free product, it may be relied on to accomplish results equivalent to those obtained from a lemon rinse. They further agreed to discontinue any statements to the effect that nonlathering oil shampoos do not rinse out of the hair, that they have little, if any, cleansing action and will not cleanse the hair or alter the natural stretch of human hair; and to cease making any other unwarranted statement which might tend to disparage or discredit competitors or their products. Further, they agreed to discontinue use of the trade designation "Northern Research Industries" for their business, or the word "Research," either alone or in combination with other words, in any manner that might give the impression that their business is a research undertaking.

Wade's Wonder Worker.—That this product will remove corns or calluses instantly or afford immediate relief from them, or that it contains ingredients not found in other preparations and is an effective treatment for bunions, chilblains, ingrowing nails, warts, rusty nail wounds, poison oak, or all skin diseases and disorders, is an adequate treatment for all deep-seated cases of athlete's foot or ringworm, or for bites or stings of poisonous insects, or can be depended on to relieve all types of toothache were misrepresentations which Cloren Richard Wade, trading as C. R. Wade Medicine Company, Hot Springs, Ark., agreed to remove from his advertising in a stipulation that he entered into with the Federal Trade Commission in August 1943. He further stipulated to discontinue any advertisement which did not clearly reveal the potential danger in using the product. It was provided, however, that if the directions for use, whether appearing in or on the labeling, contain adequate and specific warnings as to the potential danger, the advertisement need bear only the statement, "Caution: Use only as directed."

Western Medical Corporation's Treatment.—This has been promoted for years to the public, chiefly by mail. In May 1943 the Federal Trade Commission reported that it had accepted a stipulation from the Western Medical Corporation of Chicago, in which the latter agreed to discontinue the following misrepresentations: That the method of treatment it offers for epilepsy is new or uncommon and that methods followed in general are "old-fashioned"; that its method of treatment will "do something more" than simply hold down epileptic attacks or that it may be expected to reach and treat the underlying causes of such attacks; that the causes of epilepsy are usually known to the physician employed by the respondent corporation and that in general such causes are inherited bodily weaknesses from ancestral disorders or diseases, injury, fright, overstudy, or a permanent weakening of the system by such afflictions as spinal meningitis, typhoid, influenza and pneumonia; and that from written answers to questionnaires the respondent corporation can obtain substantially "complete" information for the adequate and effective treatment of a

case of epilepsy. According to the Commission, the preparations sold by the respondent contained such drugs as thyroid extract, zinc phosphide, bromides, laxatives or phenobarbital, which, the stipulation states, are dangerous to health if used in too frequent or too large doses or for extended periods of time. The corporation agreed to discontinue any advertising which failed clearly to reveal that such ingredients are potentially dangerous to the health of the user. It was provided, however, that it would be sufficient for the advertising to warn: "Caution, Use Only as Directed" when the directions on the labels contained an adequate and specific warning as to the potential dangers mentioned above.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

NATIONAL BOARD OF MEDICAL EXAMINERS EXAMINING BOARDS IN SPECIALTIES

Examinations of the Examining Boards in Specialties were published in THE JOURNAL, July 29, page 931.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: Montgomery, Oct. 24-26. Sec., Dr. B. F. Austin, 519 Dexter Ave., Montgomery.

ALASKA: Juneau, September 5. Sec., Dr. W. M. Whitehead, Box 561, Juneau.

DELAWARE: Dover, Oct. 10-12. Sec., Medical Council of Delaware, Dr. J. S. McDaniel, 229 S. State St., Dover.

DISTRICT OF COLUMBIA: * Washington, November. Sec., Commission on Licensure, Dr. G. C. Ruhland, 6150 E. Municipal Bldg., Washington.

INDIANA: Indianapolis, Jan. 3-5. Exec. Sec., Board of Medical Registration and Examination, Miss Ruth V. Kirk, 301 State House, Indianapolis 4.

IOWA: * Iowa City, Sept. 25-27. Dir. Division of Licensure and Registration, Mr. H. W. Grefe, Capitol Bldg., Des Moines.

KANSAS: Nov. 2-3 Sec., Board of Medical Registration and Examination, Dr. J. F. Hassig, 905 N. Seventh St., Kansas City.

KENTUCKY: Louisville, Sept. 11-12. Sec., State Board of Health, Dr. Philip E. Blackerby, 620 S. Third St., Louisville.

LOUISIANA: Sept. 7-9. Sec., Dr. R. B. Harrison, 1507 Hibernia Bank Bldg., New Orleans.

MINNESOTA: * Minneapolis, Aug. 29-31. Sec., Dr. J. F. Du Bois, 230 Lowry Medical Arts Bldg., St. Paul.

MISSOURI: St. Louis, Sept. 18-20. Sec., State Board of Health, Dr. James Stewart, State Capitol Bldg., Jefferson City.

MONTANA: Helena, Oct. 2-4. Sec., Dr. O. G. Klein, First Nat'l. Bank Bldg., Helena.

NEBRASKA: * Omaha, Sept. 26-28. Dir., Bureau of Examining Boards, Mr. Oscar F. Humble, 1009 State Capitol Bldg., Lincoln.

NEW HAMPSHIRE: Concord, Sept. 14-15. Sec., Board of Registration in Medicine, Dr. D. G. Smith, 77 Main St., Nashua.

NEW MEXICO: * Santa Fe, Oct. 9-10. Sec., Dr. LeGrand Ward, 141 Palace Ave., Santa Fe.

NORTH CAROLINA: Raleigh, Sept. 11-12. Sec., Dr. W. D. James, Hamlet.

OHIO: *Examination.* Columbus, Sept. 26-29. *Endorsement.* Columbus, Oct. 3. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.

OKLAHOMA: * Oklahoma City, Sept. 16. Sec., Dr. J. D. Osborn, Jr., Frederick.

SOUTH CAROLINA: Charleston, Sept. 11-13. Sec., Dr. N. B. Heyward, 1329 Blandena St., Columbia.

UTAH: Salt Lake City, Sept. 20-22. Asst. Dir., Department of Registration, Miss Rena B. Loomis, 324 State Capitol Bldg., Salt Lake City.

VERMONT: Burlington, Sept. 12-14. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: Richmond, Sept. 19-22. Sec., Dr. J. W. Preston, 30½ Franklin Rd., Roanoke.

WEST VIRGINIA: Charleston, Oct. 2-4. Commissioner, Public Health Council, Dr. John E. Offner, State Capitol, Charleston 5.

* Basic Science Certificate required.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

DISTRICT OF COLUMBIA: Washington, October. Sec., Commission on Licensure, Dr. G. C. Ruhland, 6150 E. Municipal Bldg., Washington.

FLORIDA: Gainesville, Nov. 4. Final date for filing application is Oct. 20. Sec., Dr. J. F. Conn, John B. Stetson University, DeLand.

MICHIGAN: Ann Arbor and Detroit, Oct. 13-14. Sec., Miss Eloise LeBeau, 101 N. Walnut St., Lansing.

OREGON: Portland, Nov. 4. Sec., Mr. C. D. Byrne, University of Oregon, Eugene.

RHODE ISLAND: Providence, Aug. 16. Chief, Division of Examiners, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

WISCONSIN: Madison, Sept. 23. Sec., Prof. R. N. Bauer, 152 W. Wisconsin Ave., Milwaukee 3.

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Federal Food, Drug and Cosmetic Act: Marmola Tablets for Obesity Misbranded.—The United States filed a libel in the federal district court, western district, Wisconsin, for the condemnation of a shipment in interstate commerce of Marmola Prescription Tablets, marketed as a cure for obesity, on the ground that the preparation was misbranded within the meaning of the Federal Food, Drug and Cosmetic Act. The Raladam Company, which marketed the preparation to wholesale and retail outlets, intervened in the proceedings. The trial court ordered that a decree of condemnation issue (*United States* v. *62 Packages More or Less, of Marmola Prescription Tablets,* 48 F. Supp. 878; J. A. M. A. **122:**702 [July 3] 1943) and the Raladam Company appealed to the circuit court of appeals, seventh circuit.

The libel filed by the federal government alleged that the preparation was misbranded within the meaning of the Federal Food, Drug and Cosmetic Act because (1) it was dangerous to health when used in the dosage or with the frequency prescribed in its labeling and (2) the labeling was false and misleading by reason of its failure to reveal facts with respect to consequences which may result from its use under the conditions of use prescribed on the label. There was present in each tablet of the preparation ½ grain (0.03 Gm.) of desiccated thyroid, containing approximately 0.3 per cent organic iodine, which is about 50 per cent more organic iodine than is present in desiccated thyroid U. S. P., producing consequently greater physiologic effect than equivalent amounts of a U. S. P. product of desiccated thyroid. It was the failure of the label adequately to conform to the provisions of the act because of the presence of the desiccated thyroid in the preparation that formed the real basis of the government's libel. According to the labeling of the preparation, it is intended as a cure for obesity and is for use only by obese persons who are otherwise normal and healthy and whose obesity is caused by hypothyroidism with accompanying subnormal metabolism. The labeling further represented that hypothyroidism is the basic cause of obesity, which results from a lack of a substance which Marmola supplies, and recommended a dose, where indicated, of four tablets daily. This daily dosage recommended is equivalent to 2 grains (0.13 Gm.) of desiccated thyroid containing 0.3 per cent organic iodine, or to 3 grains (0.2 Gm.) of desiccated thyroid containing 0.2 per cent organic iodine in a U. S. P. product. The trial court found under the circumstances that the Federal Food, Drug and Cosmetic Act had been violated because Marmola tablets, when used in the dosage and with the frequency, and for the duration prescribed, recommended or suggested in their labeling are dangerous to health. The circular accompanying each bottle of Marmola recommended that the user take one Marmola tablet before each meal and one at bedtime over a period of sixty to ninety-days—if needed that long. The circular advised the user to stop taking Marmola if he or she lost abnormal excess weight if later weight was redeemed and to resume the taking of Marmola tablets until conditions are corrected and to consult the user's physician if any unusual circumstances or conditions arise.

The essential question in this case, said the circuit court of appeals, is whether the evidence before the trial court is such as to justify us in saying as a matter of law that the trial court's finding that the Federal Food, Drug and Cosmetic Act had been violated because Marmola Tablets when used in the dosage and with the frequency and for the duration prescribed, recommended or suggested in their labeling are dangerous to health is erroneous. Obviously, said the court, the trial court's finding should not be set aside unless clearly against the weight of the evidence. The Raladam Company has sold this concoction for more than thirty years as a reducing aid for persons whose obesity is supposed to be caused by hypothyroidism and

who have an accompanying subnormal metabolism. "Hypothyroidism," resulting from underfunctioning of the thyroid gland, is accompanied by a subnormal metabolic rate and such symptoms as dryness of the skin, scarcity of hair and eyebrows, sluggishness of physical and mental reactions, decreased appetite, slower pulse rate and characteristic changes in the composition of the blood, and, in advanced stages, by a puffy and swollen appearance of the face and other parts of the body due, not to increased fatty tissue, but to mucoid fluid deposited beneath the skin. "Metabolism" denotes the sum total of all processes of the human body by which food is transformed into chemicals in turn absorbed into the blood stream and lymphatic system for the purpose of so nourishing the body that it can continue to function. In other words, it is the aggregate of all processes whereby food is digested, heat and energy created, the body built up or repaired and waste matter excreted. By examination of the rates at which normal persons give off heat, scientists have established the normal rate of metabolism from which, experience has revealed, most persons deviate by not more than 10 per cent. To enjoy good health, one's body must maintain a proper balance of essential chemicals; the thyroid gland is the primary agency in achievement of this end. Excess of the thyroid hormone in the blood stream results in hyperthyroidism and too little in hypothyroidism. The only ingredient of the condemned drug with which the proceeding was concerned is the desiccated thyroid included in the formula. This is derived from the glands of hogs and sheep and has the same effect on one's physical makeup as the hormones produced by a human gland. The potency of desiccated thyroid is roughly proportional to its iodine content. The product here contains approximately 0.3 per cent of organic iodine and thus possesses one and one-half times the potency of that made in accord with the standard of the U. S. Pharmacopeia.

At the trial, continued the court, qualified authorities and specialists in medicine, chemistry and nutrition supplied testimony, somewhat in conflict, relating to the cause and "cure" for obesity, hypothyroidism and hyperthyroidism and to metabolism, as well as proof of the effect of thyroxin on persons suffering from Graves' disease, heart disease, amenorrhea and psychoneuroses. The evidence disclosed that an overdosage of desiccated thyroid produces hyperthyroidism. Indeed, as to this there can be no question, since such medication supplies an excess of the hormone. The record also reveals that medical men are in agreement that one person's tolerance for the drug may be a great deal less than another's. The Raladam Company recognizes this too, since in the circular it warns "No food, drug or other substance which has any physiological effect may be taken internally or applied externally without the possibility of unpleasant or harmful results in some persons if they happen to be constituted so that they do not tolerate the food or other substance. . . . If any unpleasant effects are experienced stop taking Marmola until they disappear." Medical witnesses testified as to further effects of overdosage, such as increased metabolism of the patient, injuriously affecting the functioning of the endocrine glands, kidneys and liver; impairment of bodily functions because of the extra burden placed on human organs; symptoms which cannot be distinguished from those peculiar to hyperthyroidism, such as rapid heart, heart pains, nervous and emotional instability, nausea, menstrual disturbances and serious aggravations which result in persons who consider themselves normal and healthy but are actually subject to such latent diseases as heart disease, diabetes or tuberculosis, when they use desiccated thyroid. Indeed, their testimony is largely to the effect that a daily dosage of 2 grains a day is dangerous to health. Lay witnesses gave vivid reports of the effect of the tablets on their health. Weakness, heart palpitations, amenorrhea, emotional nervous states and domestic difficulties were described as aftermaths of the use of the tablets.

We think, continued the court, that the evidence adduced before the trial court was such as to justify only the conclusion reached by that court and we certainly are not justified in saying that the finding is erroneous as a matter of law. Admittedly, taking four tablets a day is not dangerous to the health of all users, since tolerance for the drug varies; but the experience of various witnesses, all of whom took tablets according to the directions on the label, as well as the testimony of a number of medical experts, inevitably impels one to the finding that use of the tablets as prescribed is dangerous to the health of the public. The fact that some users may be able to tolerate greater quantities does not militate against the conclusion for the Federal Food, Drug and Cosmetic Act does not require that the drug be dangerous to the health of all who take it in the dosage and for the duration prescribed or recommended. It devolved on the trial court to determine only whether it was proved that the drug is dangerous to the public health at large if used as recommended by its vendors.

The trial court, said the appellate court, further found that the Marmola tablets were subject to condemnation in that they were misbranded because they were falsely represented to be a safe and appropriate remedy for obesity, when in fact they are not, because obesity is not caused by the lack of any substance which Marmola supplies, and in that the labeling did not reveal facts material with respect to possible consequences of use of the tablets under the conditions prescribed, since the instruction to discontinue use of the tablets on appearance of "unpleasant effects" does not prevent the occurrence of more serious symptoms as a result of the hyperthyroidic condition previously precipitated.

The Raladam Company, said the court, attempts to make much of the proposition that the legislative history of the Federal Food, Drug and Cosmetic Act discloses that Congress had no intent to deprive individuals of the right of self medication. This we think beyond the point, for the decision of the lower court deprives no one of this right. It merely determines that Marmola tablets are dangerous to the public health when used in the dosage and with the frequency prescribed by its manufacturers. What would be a nondeleterious prescription was not agreed on by the experts testifying at the trial and was not within the province of the court to decide.

Accordingly, the judgment of condemnation was affirmed.—*United States* v. *62 Packages, More or Less, of Marmola Prescription Tablets, 142 F. (2d) 107 (1944).*

Society Proceedings

COMING MEETINGS

Aero Medical Association of the United States, St. Louis, Sept. 4-6. Dr. David S. Brachman, 5440 Cass Ave., Detroit 2, Secretary.

American Congress of Physical Therapy, Cleveland, Sept. 6-9. Dr. Richard Kovacs, 2 East 88th St., New York 28, Secretary.

American Hospital Association, Cleveland, Oct. 2-6. Mr. George P. Bugbee, 18 East Division St., Chicago, Executive Secretary.

American Pediatric Society, Atlantic City, N. J., Sept. 25-27. Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis 8, Secretary.

American Public Health Association, New York, Oct. 3-5. Dr. Reginald M. Atwater, 1790 Broadway, New York 19, Executive Secretary.

American Roentgen Ray Society, Chicago, Sept. 24-29. Dr. H. Dabney Kerr, University Hospitals, Iowa City, Secretary.

Colorado State Medical Society, Denver, Sept. 27-29. Dr. John S. Bouslog, 537 Republic Bldg., Denver 2, Secretary.

Delaware, Medical Society of, Lewes, Sept. 11-12. Dr. W. O. La Motte, 601 Delaware Avenue, Wilmington, Secretary.

District of Columbia, Medical Society of the, Washington, Oct. 5-7. Mr. Theodore Wiprud, 1718 M St. N.W., Washington, Secretary.

Indiana State Medical Association, Indianapolis, Oct. 3-5. Mr. T. A. Hendricks, 23 East Ohio St., Indianapolis 4, Executive Secretary.

International College of Surgeons, U. S. Chapter, Philadelphia, Oct. 3-5. Dr. Desiderio Roman, 250 South 17th St., Philadelphia, Secretary.

Kentucky State Medical Association, Lexington, September 18-20. Dr. P. E. Blackerby, 620 S. Third St., Louisville, Secretary.

Michigan State Medical Society, Grand Rapids, Sept. 27-29. Dr. L. Fernald Foster, 2020 Olds Tower, Lansing 8, Secretary.

Mississippi Valley Medical Society, Peoria, Ill., Sept. 27-28. Dr. Harold Swanberg, 510 Maine St., Quincy, Ill., Secretary.

National Medical Association, St. Louis, Aug. 14-17. Dr. John T. Givens, 1108 Church St., Norfolk, Va., Secretary.

Northern Minnesota Medical Association, Hibbing, Aug. 26. Dr. R. N. Jones, 8 Sixth Ave. N., St. Cloud, Secretary.

Oregon State Medical Society, Portland, Sept. 2-3. Dr. Thomas D. Robertson, St. Vincent's Hospital, Portland, Secretary.

Pennsylvania, Medical Society of the State of, Pittsburgh, Sept. 19-21. Dr. Walter F. Donaldson, 500 Penn Ave., Pittsburgh 22, Secretary.

Radiological Society of North America, Chicago, Sept. 24-29. Dr. Donald S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y., Secretary.

Utah State Medical Association, Salt Lake City, August 24-26. Dr. D. G. Edmunds, 610 McIntyre Bldg., Salt Lake City, Secretary.

Wisconsin, State Medical Society of, Milwaukee, Sept. 18-20. Mr. Charles H. Crownhart, 110 E. Main St., Madison 3, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1934 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Diseases of Children, Chicago

67:341-428 (May) 1944

Deficiency Anemia in Infants: Report of 2 Cases, with Associated Temporary Deficiency of Antianemic Factor in 1 and Allergic and Abnormal Digestion of Protein in the Other. M. H. Bass.—p. 341.
Serum Phosphatase Activity and Clinical Rickets in Children in Jerusalem. R. Klasmer.—p. 348.
*Cystic Fibrosis of Pancreas: Report of 18 Proved Cases. Maud L. Menten and T. O. Middleton.—p. 355.
Fatal Effects of Prolonged Complete Curarization. M. A. Perlstein and A. Weinglass.—p. 360.
*Studies on Control of Acute Infections of Respiratory Tract: III. Results of Sulfadiazine Therapy from May 3, 1942 to May 2, 1943. M. Siegel.—p. 365.
Serum Tocopherol: Its Relation to Failure of Vitamin E Therapy for Pseudohypertrophic Muscular Dystrophy. A. S. Minot and Helen E. Frank.—p. 371.
Ascorbic Acid, Riboflavin and Thiamine Content of Cow's Milk. A. D. Holmes, C. P. Jones and Anne W. Wertz.—p. 376.
Poliomyelitis: II. Results of Treatment During Acute Stages of Disease. J. A. Toomey and P. M. Kohn.—p. 393.

Cystic Fibrosis of Pancreas.—According to Menten and Middleton children suffering from cystic fibrosis of the pancreas show failure to gain weight, wasting, vomiting, diarrhea or constipation, protuberant abdomen, bulky fatty intestinal contents, cough and terminal bronchopneumonia. They report 18 cases in which diffuse definite dilatation of the pancreatic acini and associated pneumonia were observed at necropsy. A clinical diagnosis of cystic fibrosis of the pancreas was made in 1 child. The 18 cases were gleaned from 640 necropsies performed at the Children's Hospital in Pittsburgh from Jan. 1, 1936 to June 1, 1943 and represent 2.8 per cent of the total number. During the same period celiac disease was diagnosed in 15 cases. Cystic fibrosis of the pancreas was diagnosed in only 3 of the cases during life, largely because of lack of presenting symptoms. No definite causes for the pancreatic changes have been found. It is probable that pancreatic lesions precede the atresia and are the cause and not the result of these rare abnormalities. The theory of fetal inflammation fails because of the absence of inflammatory cells and the presence of normal islet tissue. Congenital syphilis may produce a pathologic picture in the pancreas approximating cystic fibrosis, but other characteristics of this disease are absent. Congenital malformations of the acini or alterations in the pancreatic secretions have not been demonstrated. The fact that there are pathologic changes in accessory pancreatic tissue in the jejunum which are identical with the changes in the main organ argues that intrinsic biochemical alterations in the acinar epithelium are probably a fundamental etiologic factor.

Sulfadiazine in Acute Infections of Respiratory Tract.—Siegel made his observations in an institution for feebleminded patients among children highly susceptible to infections of the respiratory tract and to secondary bacterial complications. The children varied in age from 2 to 15 years, the average being 8.1 years. A group of about 130 girls lived in cottage Y and an approximately equal number of boys in cottage Iota. New admissions to each cottage replaced withdrawals at the rate of about 1 per week. The duration of residence varied considerably. The children were assigned to the control or to the sulfadiazine treated group in alternate order of admission. The groups were comparable with regard to age, weight, frequency of mongolism and past incidence of pneumonia and other acute infections of the respiratory tract. The children in the two groups were managed alike, except for the use of sulfadiazine in the treated group at the onset of clinical infections of the respiratory tract. The period of observation lasted from May 1942 to May 1943. During these periods 250 acute infections of the respiratory tract were studied in 130 patients. The results obtained are similar to those noted during the first six months of the study, which were reported previously. The illnesses were milder in the drug treated groups than in the untreated groups, with the exceptions noted in outbreaks of infections presumably of virus origin and in sporadic infections. The beneficial effects were attributed to the bacteriostatic action of sulfadiazine. The differences observed between the untreated and the treated groups varied considerably. Although the severity of the illnesses in the control group fluctuated with the year to year variations in severity of infections prevalent at the time, the infections in the treated group appeared to be relatively mild. The drug seemed to exert a stabilizing effect on the course of acute infections of the respiratory tract. Such an effect might prove to be of value during severe outbreaks of influenza and other respiratory diseases in which drug susceptible bacteria may be primarily or secondarily implicated.

American Journal of Physiology, Baltimore

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*Relationship of Copper to Hematopoiesis in Experimental Hemorrhagic Anemia. A. R. Maass, L. Michaud, H. Spector, C. A. Elvehjem and E. B. Hart.—p. 322.
*Study of Gelatin and Saline as Plasma Substitutes. W. W. Swingle, W. Kleinberg and H. W. Hays.—p. 329.
Mode of Action of Anticoagulant Derived from Tissues. G. J. de Sütö-Nagy.—p. 338.
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Depressor Effects of Cold on Static Receptors of Labyrinth. E. Spiegel.—p. 404.
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Effect of Sodium and Potassium Chloride on Renal Clearance of Ascorbic Acid. E. E. Selkurt and C. R. Houck.—p. 423.
Mechanism of Sucrose Damage of Kidney Tubules. H. A. Wilmer.—p. 431.

Copper and Hemopoiesis in Experimental Hemorrhagic Anemia.—Maass and his collaborators report studies on young growing dogs which were kept on a raw milk diet supplemented with crystalline B vitamins and manganese and rendered anemic by bleeding. Blood analysis showed a characteristic picture of secondary anemia. The anemia showed no response to dietary supplementation of iron in the absence of copper. The daily administration of 3 mg. of copper brought about an immediate and rapid increase in hemoglobin, hematocrit and red cell counts to normal values. An iron deficiency in the presence of adequate (3 mg.) copper caused a nutritional anemia and a concomitant decrease in mean corpuscular volume. The administration of 10, 20 or 30 mg. of iron with 3 mg. of copper gave the characteristic remission in the anemic dogs.

Gelatin and Saline Solution as Plasma Substitutes.—Swingle and his associates found that the application of a Duncan-Blalock press to one hind leg of a deeply anesthetized dog for seven hours at 750 pounds pressure induced fatal shock in 25 of 26 untreated control animals. The average survival period following release of the press was eleven hours. The shock is characterized by intense hemoconcentration, progressive fall in arterial pressure and loss of plasma. There is an average decline in plasma volume of 48 per cent. The greatly swollen leg indicated that most if not all of the plasma volume decline could be accounted for by plasma loss into the injured area. A

single massive intravenous infusion of gelatin, representing 40 cc. per kilogram, given immediately after removal of the leg press, failed to prevent fatal shock in 10 of 11 dogs. The gelatin was apparently not retained in the circulation but rapidly passed through the injured capillaries of the limb. Six intermittent gelatin infusions of 6.6 cc. per kilogram each, administered over an eight hour interval from the time of removing the leg press, prevented shock in 19 of 26 animals. Intermittent infusions of 0.9 per cent saline solution, administered in equal dosage and over the same time interval as the gelatin, proved to be less effective. Eight of 23 dogs survived, whereas 15 died. Small intermittent infusions of pooled, heparinized dog plasma administered in the same dosage and over the same time interval proved no more effective in preventing shock than similar infusions of gelatin. The authors conclude that intermittent infusions of plasma or plasma substitutes, when given in small amounts over a period of hours, are more effective in preventing shock than is a single massive infusion.

Am. J. Syphilis, Gonorrhea and Ven. Dis., St. Louis

28:265-396 (May) 1944

*Rapid Treatment of Neurosyphilis with Malaria and Chemotherapy. B. Dattner, E. W. Thomas and Gertrude Wexler.—p. 265.
Canada's First National Venereal Disease Control Conference. D. H. Williams.—p. 286.
*Induction of Fever by Intravenous Infusion of Triple Typhoid Vaccine in Treatment of Syphilis. H. Lawrence.—p. 289.
Unusual Behavior of Syphilitic Reagin Following Intensive Treatment of Early Syphilis. A. G. Schoch and L. J. Alexander.—p. 305.
Epidemic of Genital Chancres from Perversion. H. Goodman.—p. 310.
Oral Use of Sulfathiazole in Prevention of Gonorrhea and Chancroid. E. E. Keet Jr.—p. 315.
Primary Cutaneous Gonococcal Lesions of External Male Genitalia. M. M. Kroll and E. M. Cohart.—p. 320.
Urethral Tyrothricin Irrigations in Male: Experimental and Clinical Study. L. Dub.—p. 325.

Malaria and Chemotherapy in Neurosyphilis.—Dattner and his associates stressed in a previous report the importance of spinal fluid examinations as the most reliable criteria for determining the activity of a syphilitic process in the central nervous system. Symptoms and signs usually associated with dementia paralytica or tabes dorsalis may occasionally be due to other causes than syphilis. In the presence of positive specific tests for syphilis the best available guide to determining the activity of a syphilitic infection of the central nervous system is increase in the cells and protein of the spinal fluid. It has been the policy at Bellevue Hospital since Jan. 1, 1939 to treat all patients whose spinal fluid is actively syphilitic, regardless of the presence or absence of clinical signs and symptoms, with some form of fever in addition to chemotherapy, unless fever is definitely contraindicated by the general condition of the patient. Fever was induced with malaria in all the patients. The number of malarial paroxysms was limited to eight. This was followed immediately by chemotherapy. At first patients were given alternate courses of weekly injections of arsenical drugs followed by bismuth for a period of six months after malaria. Later the authors shortened the period of treatment by giving one injection of 0.06 Gm. of mapharsen daily for ten days following the last fever, while the patient was still in the hospital ward. No significant differences were noted in the two groups. The spinal fluid was examined six months after the completion of therapy. If this showed no more than 4 cells per cubic millimeter and definite reduction in protein content, no further antisyphilitic treatment was given. The patients were kept under observation, and spinal fluids were examined every six months. Patients whose spinal fluids still showed signs of activity six months after treatment were either returned to the hospital wards for retreatment or given some type of chemotherapy. Of the 419 patients who received 424 treatment courses 10 died, 62 are lost and 54 have been treated too recently for evaluation. The report of the results of therapy is limited to 293 patients, or 298 treatment courses. Of the patients who were followed from six to forty-eight months 85.9 per cent showed satisfactory results.

Triple Typhoid Vaccine in Treatment of Syphilis.—According to Lawrence, arsenical toxicity is diminished when fever is given with chemotherapy. The combination of fever and intensive chemotherapy requires less arsenic for the same therapeutic efficiency than does chemotherapy unaccompanied by fever. Patients who have had arsenical exfoliative dermatitis can tolerate further arsenicals if these are given in combination with fever therapy. The technic employed consisted of a continuous infusion of typhoid vaccine in a saline suspension as described by Solomon and Somkin. The infusion was prepared by adding the selected amount of army triple typhoid vaccine to 1 liter of saline solution, which was then shaken thoroughly. The solution was administered intravenously by an Abbott drip infusion apparatus. When it was clear that fever produced by this technic was well tolerated even when combined with chemotherapy, 0.06 Gm. of mapharsen was given intravenously with every paroxysm of fever in all subsequent treatments. Twice a week, on days on which fever was not given, 0.13 Gm. of bismuth subsalicylate in oil was injected intramuscularly. Forty hours above 104 F. was considered to be the optimum amount of fever for a course. Approximately ten treatments of four hours each above 104 F. was the method by which this was obtained. To date 10 patients have been treated by the infusion of triple typhoid vaccine without serious complication. No manifestations appeared of tetany, cerebral edema, dehydration or cardiac failure. The two instances of vasomotor collapse responded readily to corrective measures. Antisyphilitic therapy with arsenicals can be given at the height of the fever; this is not possible in malaria therapy. The necessity of continuously administering oxygen, as recommended in the use of a fever cabinet, was eliminated. It was gratifying to be able to maintain a patient for eight hours between 104 and 106 F. during the day and see him up and about the ward that evening. Because of its simplicity this technic of inducing fever is especially suited to army facilities.

Annals of Surgery, Philadelphia

119:641-800 (May) 1944

Surgical Lesions of Facial Nerve, with Comments on its Anatomy. C. C. Coleman.—p. 641.
Diverticula of Urinary Bladder. E. Burns.—p. 656.
*Thyroid Carcinoma with Metastases Studied with Radioactive Iodine. V. K. Frantz, R. P. Ball, A. S. Keston and W. W. Palmer.—p. 668.
Modified Technic in Skin Grafting of Extensive Deep Burns. H. Saltonstall and W. E. Lee.—p. 690.
Further Experience with Treatment of Burns with Sulfonamide Impregnated Membranes. W. DeW. Andrus and J. A. Dingwall III.—p. 694.
*Primary Hemangiomatous Tumors of Skeletal Muscle. T. A. Shallow, S. A. Eger and F. B. Wagner.—p. 700.
Acute Retroperitoneal Abscess and Phlegmon. H. Neuhof and E. E. Arnheim.—p. 741.
*Annular Pancreas Producing Duodenal Obstruction. R. E. Gross and T. C. Chisholm.—p. 759.
Conservative Treatment of Acute Duodenal Fistula. M. J. Thorstad.—p. 770.
Rare Abnormality of Bile Ducts: Anteduodenal Position of Cystic Duct. P. Campiche.—p. 774.
Treatment of Horseshoe Kidneys. O. S. Culp.—p. 777.
Wilms Tumor in a Horseshoe Kidney. E. L. Eliason and L. W. Stevens.—p. 788.
Crude Penicillin: Its Preparation and Clinical Use Externally. Charlotte Dunayer, Lillian Buxbaum and Hilda Knobloch.—p. 791.
Postoperative Chronic Progressive Gangrene of Abdominal Wall. M. Davison, B. G. Sarnat and E. Lampert.—p. 796.

Radioactive Iodine in Thyroid Carcinoma.—Frantz and his associates reported in 1942 an instance of storage of radioactive iodine in a metastasis from a thyroid carcinoma. They now present a completed report of this case, observed until death. When the radioactive isotope of iodine became available, it afforded an easy method of checking iodine storage in metastases from thyroid carcinoma. The radioactive iodine produced by the cyclotron is mixed with inert iodine compounds such as potassium iodide and is usually administered by mouth. The patient, a Negro woman aged 39, first complained of swelling of the neck of seven years' duration in 1934. At this time a vascular tumor was removed from the isthmus of the thyroid. In 1941, seven years after operation and fourteen years after the tumor was first noticed, the patient sustained a pathologic fracture of the left humerus. A roentgenogram showed areas of bone destruction in the shaft of the humerus near the deltoid tubercle, and a small fracture line on the medial border. There was a soft, pulsating oval tumor about 8 cm. in diameter projecting 4 cm. above the scalp in the region of the left parietal bone. Further roentgenograms showed areas of bone destruc-

tion in the lower end of the right femur and in the left parietal bone. Roentgen irradiation was applied to the lesion of the humerus and later to the thigh and to the tumor of the parietal bone. Roentgen treatment of the latter two regions was interrupted for the administration of a tracer dose of radioactive iodine, which was given orally in water. The substance was taken up, as shown by the Geiger counter, in considerable quantity by the metastasis in the right femur and by the thyroid but not by the other bony metastases. It was suggested that a larger dose might afford selective therapeutic "internal irradiation," and 10 millicuries was given. The right femoral metastasis showed no change in radioactive iodine content during the first week, but when measured again at the end of three weeks it showed loss of 85 per cent of its radioactive iodine. A tracer dose given a few days later showed no further uptake by the metastasis, although there was new localization in the thyroid. This was interpreted at the time as evidence of the effectiveness of this "internal irradiation." The patient died. At necropsy the bulk of the metastatic tissue was undifferentiated. The metastasis which showed consistent uptake of iodine was the only one which grossly resembled thyroid tissue and which microscopically showed well differentiated tumor. The authors know of no evidence that external irradiation of thyroid carcinoma may change the microscopic character of the tumor. They believe that two types of tumor were present. There was no uptake of radioactive iodine in most of the lesions. Since some well differentiated tumors of the thyroid are capable of storing iodine, it is thought that in selected cases therapeutic internal irradiation of metastases may be achieved with large enough doses of radioactive iodine. Tracer doses of iodine may be valuable diagnostically. Failure of uptake does not mean that the tumor is not of thyroid origin.

Primary Hemangiomatous Tumors of Skeletal Muscle.—Shallow and his associates report 2 cases of primary hemangiomatous tumors of skeletal muscle. A woman aged 35 noted over a period of five years a slowly growing mass on the lateral aspect of her left thigh which pulsated, had a bruit and was unassociated with any symptoms except slight pain. Temporary ligation of the left common iliac artery was followed up by wide excision of a partially circumscribed hemangioendothelioma involving three contiguous muscles. Postoperative high voltage roentgenotherapy was given. Complete recovery ensued without loss of function. The second patient was a boy aged 10 years who noticed a lump on the inner aspect of his right arm following trauma. The lump increased in size and became painful. Physical examination revealed a soft, tender, walnut sized mass over which a bruit could be heard. A cavernous hemangioma involving the medial head of the triceps muscle was removed at operation. During the next two years a mass gradually appeared on the posterior aspect of the arm, accompanied by pain and limitation of extension of the forearm. Wide excision was followed by primary wound healing and complete restoration of function. The author presents an analytic review of 335 cases of primary hemangiomatous tumors of skeletal muscle. The disease occurs about equally in the two sexes and most frequently (85 per cent) during the first three decades of life. The prevailing view is that hemangiomas are congenital tumors originating from abnormal embryonic sequestrations of vascular tissue. Trauma and systemic infection, acting as secondary factors, may modify subsequent growth. The lesion arises in the vascular plexus of the muscle or in the perimysium between the muscle fibers and often resembles a muscle containing varicose veins. The tumor consists of vascular elements in a connective tissue stroma and is classified as cavernous, capillary, venous or arterial. Although pure types seldom exist, the cavernous variety is the most common. Growth is by a multicentric proliferation of endothelial cells forming vascular channels with practically no tendency to anastomose with the normal vessels in the invaded tissue. There are no proved cases of metastasis from a primary muscle hemangioma. The diagnosis was correctly made in only 19 per cent of the cases. The history usually reveals a clinical onset early in life, often following trauma to the part. The thigh is most commonly involved, especially the quadriceps femoris muscle. The diagnosis may be confirmed by aspiration of blood from the tumor and by the presence of phleboliths on roentgenologic examination. Angiography may also be employed as an adjunct in diagnosis. The procedure of choice in treatment is early complete surgical excision well beyond the confines of the tumor. This was the treatment employed in 79 per cent of the cases, with improvement or cure in 90 per cent. In cases in which malignant degeneration is suspected, postoperative high voltage roentgenotherapy is advocated. There was no surgical mortality. Local recurrence or lack of improvement was reported in 6 per cent of the cases and postoperative deformity in 4 per cent.

Annular Pancreas Producing Obstruction.—A newborn infant with evidence of duodenal obstruction came recently under the care of Gross and Chisholm. Roentgenologic examination with the child in the recumbent position showed some dilatation of the stomach and a bubble of gas in the right upper quadrant of the abdomen, which was assumed to be air in a dilated first portion of the duodenum. No gas could be found in any other part of the abdomen. These findings were interpreted as representing a complete obstruction of the duodenum. The malformation was found at operation. The authors left the local abnormality undisturbed and performed a side to side duodenojejunostomy. The jejunum was brought upward and laid against the anterior wall of the dilated first portion of the duodenum so that an isoperistaltic type of anastomosis could be established. The baby was discharged from the hospital on the sixth postoperative day. There was no vomiting; she was taking her feedings well. Subsequent development of the child has been normal. The constriction of the duodenum is not always sufficient to cause clinical symptoms. If symptoms of duodenal obstruction appear they should be relieved by surgical correction. Operative alleviation of the obstruction has been practiced by (1) division of the pancreatic ring, (2) posterior gastroenterostomy or (3) duodenojejunostomy. The authors believe that the first procedure is the least desirable and that the last one is the operation of choice. The case described is the only one which has ever been treated by this method.

Archives of Neurology and Psychiatry, Chicago

51:415-500 (May) 1944

Electromyography as Method for Determination of Level of Lesions in Spinal Cord. P. F. A. Hoefer and S. A. Guttman.—p. 415.
Incidence of Metastases to Nervous System. M. Neustaedter.—p. 423.
*Torular Granuloma Simulating Cerebral Tumor: Report of 2 Cases. H. S. Swanson and W. A. Smith.—p. 426.
The Scalenus Anticus Syndrome: Types; Their Characterization, Diagnosis and Treatment. R. L. Swank and F. A. Simeone.—p. 432.
Effect of Glutamic Acid and Other Amino Acids on Maze Learning in White Rat. F. T. Zimmerman and S. Ross.—p. 446.
Eosinophilic Granuloma of Bone Presenting Neurologic Signs and Symptoms: Report of Case. R. L. Osborne, E. D. Freis and A. G. Levin.—p. 452.
Androgen Therapy for Involutional Melancholia. L. Danziger, H. T. Schroeder and A. A. Unger.—p. 457.
*Specific Treatment of Psychosis Due to Estrogen Deficiency. L. Danziger.—p. 462.
Biochemical Studies on Patients with Schizophrenia: Dextrose, Oxygen and Carbon Dioxide Contents of Arterial and Venous Blood from Cranial Cavity. S. Katzenelbogen, R. J. Haws and Rebecca Snyder.—p. 469.
Cerebral Metabolism in Hypoxia. E. S. Gurdjian, W. E. Stone and J. E. Webster.—p. 472.

Torular Granuloma Simulating Cerebral Tumor.—Swanson and Smith state that, although meningitis is emphasized as a common lesion of torular infections, it is not generally recognized that torulosis of the brain may simulate an intracranial tumor. The authors describe 2 cases of this type. A woman aged 49 was admitted to the hospital in the terminal stage of a progressive disease suggestive of an expanding intracranial lesion. She died before operation could be carried out. Necropsy showed three distinct, large, isolated tumor masses in the brain which grossly suggested metastatic colloid carcinoma. Microscopic studies revealed the true nature of the disease process. The second patient, a white man aged 36, had a history of proved torular infection of the lung. He presented the clinical picture of increased intracranial pressure, with localizing signs pointing to the posterior fossa. The presence of an infection of the central nervous system similar to that in the

preceding case was considered, but repeated studies of the spinal fluid showed that the cell count and the sugar content were normal and cultures negative for the organism. This indicates that changes in the spinal fluid may not appear for weeks after the onset of symptoms. In 2 typical instances of meningitis recently encountered the organisms were grown with ease from the spinal fluid as well as from the blood, urine and sputum. Roentgenographic examination of the chest showed no demonstrable lesions in either of these cases or in case 1 of this report. Roentgenographic examination of the chest is advisable in all cases in which cerebral tumor is suspected, and it may occasionally give a clue to torular infection. The cerebral lesion of torulosis may resemble a glial tumor; only section of the "tumor" reveals the characteristic appearance of a multiloculated cyst filled with gelatinous material. This "tumor" is unlike true cystic tumors in that the cavities do not empty themselves when opened. This is the most striking feature of the torular granuloma. The tendency to isolation and sharp demarcation from the adjacent cortex, together with the absence of reaction in the surrounding tissue, is another striking feature of torular granuloma, but there exists the danger that the cyst will be opened unawares and meningitis initiated. The authors believe that this was done in case 2.

Treatment of Psychosis Due to Estrogen Deficiency.—Danziger presents an analysis of 164 cases of involutional melancholia in which estrogen therapy was employed. Among these 164 women there were probably many in whom the psychosis developed either before or many years after the onset of the menopause. Such patients could not reasonably be supposed to be suffering from a psychosis due to estrogen deficiency and could not reasonably be expected to recover with estrogen therapy. The author classifies the patients into two groups, depending on whether estrogen deficiency was or was not involved. With patients whose psychosis was due to estrogen deficiency large doses of estrogen gave better results than small doses. Where psychosis was not clearly attributed to endocrine disturbances, the results did not vary with the dose. With patients in the first group, large doses gave results of the order of magnitude to be expected from specific therapy. With patients in the second group, results to be expected from specific therapy were never attained regardless of the dose. Although the two groups were not homogeneous as to the cause of their psychosis, they were both grouped according to the Statistical Manual of the National Association for Mental Hygiene under "involutional melancholia." The author suggests that the term "involutional melancholia" be replaced by "psychosis due to estrogen deficiency." In the absence of accurate evidence of disturbances in the climacteric immediately preceding the psychosis, the chances of recovery with estrogen therapy are not better than even, although the clinical picture may be that of involutional melancholia. If such patients are given estrogen therapy, their chances of prompt improvement are much better than if they do not receive special treatment.

Archives of Pathology, Chicago

37:297-350 (May) 1944

Foam Cell Plaques in Intima of Irradiated Small Arteries (100 to 500 Microns in External Diameter). J. F. Sheehan.—p. 297.
Maduromycosis of Hand, with Special Reference to Heretofore Undescribed Foreign Body Granulomas Formed Around Disintegrated Chlamydospores. D. Symmers and A. Sporer.—p. 309.
Studies in Vitro on Physiology of Normal and of Cancerous Cells: II. Survival and Glycolysis of Cells Under Aerobic and Under Anaerobic Conditions. R. Schrek.—p. 319.
New Method of Feeding Cholesterol to Animals. O. J. Pollak.—p. 337.
Automatic Staining of Routine Tissue Sections with Hematoxylin and Eosin. M. N. Richter.—p. 338.

California and Western Medicine, San Francisco

60:233-272 (May) 1944

Medical Care of Migratory Agricultural Workers: Story of Accomplishment; Presidential Address. K. L. Schaupp.—p. 238.
Public Opinion Concerning Medical Practice: An Interpretative Report on a California Survey. J. R. Little.—p. 241.
California Procurement and Assignment Service. E. M. Pallette.—p. 245.
Open Sesame! On Postgraduate Schooling. M. Wolfson.—p. 246.
Anesthesia for Military Needs. L. K. Mantell and C. F. McCuskey.—p. 247.
Dehydrated Food in War and Peace. F. DeEds.—p. 250.

Diseases of Chest, Chicago

10:171-276 (May-June) 1944

Primary Atypical Pneumonia Simulating Infiltrative Pulmonary Tuberculosis. A. L. Kruger, A. W. Wallace, J. P. Medelman and S. B. Grimes.—p. 171.
Mechanism of Hypertrophic Pulmonary Emphysema. I. Gordon.—p. 180.
Tuberculosis in Children and Young Adults. C. A. Stewart.—p. 190.
Occurrence of Pulmonary Tuberculosis in Supposedly Screened Selectees. A. Freer.—p. 197.
Tuberculosis as Navy Problem. D. F. Smiley and H. A. Raskin.—p. 210.
Study of Rejectees for Thoracic Abnormalities. W. A. Hudson and D. S. Brachman.—p. 234.
*Problem of Tuberculosis in Apparently Healthy Man as Shown in Routine Examinations for Induction into Armed Forces. C. H. Marcy.—p. 241.
Postwar Teaching of Tuberculosis. C. M. Hendricks.—p. 246.

Tuberculosis in Routine Examinations for Induction.—Marcy points out that the requirement of a routine chest roentgenogram by military authorities has resulted in the biggest tuberculosis case finding program ever attempted. The government has set a high standard of disqualifying lesions in its determined effort to keep tuberculosis at a minimum in the armed forces. The disqualified men are reported to the state health departments and then referred to their family physicians or to tuberculosis clinics for further observation and treatment. The rejectees fall into three groups. The first group includes those with minimal healed disease, probably not of clinical significance but of a degree not acceptable to the Army. In most instances they can return to their regular occupations. Such a diagnosis of tuberculosis without a detailed explanation of its significance is unfair to the men examined. In order to dispel any undue fear, they must be given an explanation of their condition. The second group is made up of men with a disease of undetermined stability. A history must be taken in order to discover whether the patient is being exposed to tuberculosis. Also previous unexplained hemoptysis or recurring pleurisy is of possible significance. Cough, expectoration, fatigue, lack of endurance and gradual loss in weight must be taken into account. Localized rales in the upper lung areas are important. Age is extremely important. Apparently healed primary tuberculosis is less significant in a man beyond 40 than it is in a youth of 18 years. Nutrition, social status, environment, habits of living and the nature of his employment together with the amount of rest must be considered. Some may need a preliminary period of hospital study, but most of them can continue at home under the guidance of their own physician. In many cases it is merely a question of establishing their work tolerance. The third group is composed of those with active tuberculosis. The majority are in an infectious stage and should have hospital care. Unless the medical profession takes an intelligent interest in the men disqualified by the military authorities because of tuberculosis, this effective case finding procedure will lose much of its value as applied to the prevention and control of tuberculosis in the civilian population.

Journal of Immunology, Baltimore

48:271-334 (May) 1944

Studies on Penicillin: II. Observations on Therapeutic Activity and Toxicity. G. Rake, Clara M. McKee, Dorothy M. Hamre and C. L. Houck.—p. 271.
Protection of Developing Chick Embryo with Specific Serum Against Infection with Shigella Paradysenteriae (Flexner). A. J. Weil and J. A. McFarlane.—p. 291.
Production of Antibrain Antibodies in Monkey. L. M. Kopeloff and N. Kopeloff.—p. 297.
Influence of Temperature of Incubation on Increase of Influenzal Virus B (Lee Strain) in Chorioallantoic Fluid of Chick Embryos. I. W. McLean Jr., Dorothy Beard, A. R. Taylor, D. G. Sharp, J. W. Beard, A. E. Feller and J. H. Dingle.—p. 305.
Volume Change Accompanying Quellung Reaction of Pneumococci. F. H. Johnson and W. L. Dennison.—p. 317.
*Effect of Paraffin Oil, Lanolin-like Substances and Killed Tubercle Bacilli on Immunization with Diphtheric Toxoid and Bact. Typhosum. J. Freund and Mary V. Bonanto.—p. 325.

Effect of Liquid Petrolatum, Lanolin-like Substances and Killed Tubercle Bacilli on Immunization Procedures.—Freund and Bonanto found that when rabbits receive injections of diphtheric toxoid incorporated in a lanolin-like substance, antitoxin formation is enhanced and prolonged as compared with antitoxin production after the injection of plain toxoid. The lanolin-like substance sustains antitoxin formation more effectively than alum. When an aqueous suspension of

killed typhoid bacilli is mixed with a lanolin-like substance and liquid petrolatum the bacteria are found in microscopic water droplets surrounded by oil. Preparations of this kind are stable. Liquid petrolatum enhances and sustains antibody formation against typhoid bacilli for a remarkably long time. Killed tubercle bacilli have an additional synergistic effect. Peanut oil has scant or no effect when compared with liquid petrolatum.

Journal-Lancet, Minneapolis

64:173-214 (June) 1944

Nutrition in Geriatric Medicine. E. L. Tuohy.—p. 173.
Abdominal Surgery in Old Age Including Comment on (1) Use of Sipper; (2) Safety of Multiple Simultaneous Operations; (3) Mechanism of Development of Bed Sores. O. H. Wangensteen.—p. 178.
Anesthesia for the Aging and Aged. R. T. Knight and J. W. Baird. —p. 183.
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The Radiologist Looks at Aging Bones. E. H. Skinner.—p. 189.
Mental Disorders of Old Age. H. D. Palmer.—p. 192.
Eye Problems in the Aged. H. W. Grant.—p. 199.
Teeth and Aging. B. N. Pippin.—p. 203.
Tuberculosis in Elderly People. A. T. Laird.—p. 208.

Journal of Neurophysiology, Springfield, Ill.

7:151-204 (May) 1944

Hind Brain and Early Development of Behavior in Frogs. G. H. Wang and T. W. Lu.—p. 151.
Reflex Inhibition of Intestinal Motility Mediated Through Decentralized Prevertebral Ganglia. A. Kuntz and G. Saccomanno.—p. 163.
Experimental Hypogeusia From Horsley-Clarke Lesions of Thalamus in Macaca Mulatta. H. D. Patton, T. C. Ruch and A. E. Walker.—p. 171.
Structural Identity of Pain Spot in Human Skin. G. H. Bishop.—p. 185.
Physiological Neuronography of Some Corticosubcortical Connections in Chimpanzee. H. W. Carol and W. S. McCulloch.—p. 199.

Journal of Pediatrics, St. Louis

24:483-602 (May) 1944

*Prophylactic Use of Sulfanilamide in Children with Inactive Rheumatic Fever. Katherine G. Dodge, Janet S. Baldwin and M. W. Weber. —p. 483.
Rheumatic Fever and Rheumatic Heart Disease in Los Angeles Children: Hospital Study. D. B. Davis and S. Rosin.—p. 502.
Rheumatic Pericarditis with Effusion in Patients Under 2 Years of Age. G. N. Krost.—p. 514.
Comparison of Diets of School Children in New York City in 1917 and 1942. Charlotte J. Evans and Rose Lubschez.—p. 518.
Seasonal Variations in Weight, Height and Appearance of Ossification Centers. E. L. Reynolds and L. W. Sontag.—p. 524.
Acute Ataxia of Unknown Origin in Children. W. O. Klingman and R. G. Hodges.—p. 536.
Ratbite Fever Caused by Streptobacillus Moniliformis: Case Report. E. Rosen and B. S. Denzer.—p. 544.
*Treatment of Pneumonia with Single Dose of Sulfadiazine. H. Vollmer, C. Abler and D. A. Rosenberg.—p. 553.
Chondrodystrophia Calcificans Congenita. M. P. Borovsky and J. Arendt. —p. 558.
Meningitis Due to Salmonella Oranienburg: Report of Case. C. H. Hollis and E. W. Barron.—p. 568.
Bezoar Causing Intestinal Obstruction. R. P. Forbes.—p. 574.
Staphylococcus Empyema in Infants and Children: Review of 29 Cases. C. M. Riley.—p. 577.

Prophylactic Use of Sulfanilamide in Inactive Rheumatic Fever.—Dodge and her associates administered sulfanilamide at Bellevue Hospital to 88 patients ranging in age from 6 to 18 years during the fall, winter and spring months for a total of 181 patient-seasons. Seven children received the drug for four seasons, 19 for three seasons, 48 for two seasons and 30 for one season. The children were given from 1 to 2 Gm. of sulfanilamide daily. One hundred and one rheumatic children were observed as controls for 138 patient-seasons. Toxic drug reactions were minimal. The drug was not discontinued permanently in any case for such a reaction. During the period of the study there were in the control group 54 hemolytic streptococcus infections, an incidence of 39 per cent. There were 19 definite major rheumatic relapses (with two deaths) and 7 mild or possible relapses. In 3 children the rheumatic process remained active throughout the period of observation, and there was one death from subacute bacterial endocarditis. In contrast to this, only 5 hemolytic streptococcus infections occurred in the group of children receiving sulfanilamide prophylaxis, an incidence of 2.7 per cent. Two children, or 1.1 per cent of the patient-seasons of prophylaxis, developed definite rheumatic relapses while taking the drug regularly. Two other children with severely damaged hearts died of congestive failure without evidence of streptococcic infection or active rheumatic disease. Two children with recently active rheumatic fever showed signs of increasing rheumatic activity within two weeks of starting the drug. The authors concluded that the effectiveness of sulfonamide prophylaxis in quiescent rheumatic fever is established and that it should be applied more widely among groups of highly susceptible individuals.

Single Dose of Sulfadiazine in Pneumonia.—Alternate children admitted with pneumonia were treated with single doses of sulfadiazine, while the others were treated with a regular course of sulfadiazine. Twenty-five children ranging in age between 8 months and 10 years were treated with a single dose. With one exception, sulfadiazine was given by mouth in a single dose of not less than 0.15 Gm. per kilogram of body weight. Smaller children weighing up to 20 Kg. received relatively higher doses, from 0.2 to 0.3 Gm. per kilogram of body weight. The maximal dose was 5.0 Gm. of sulfadiazine. Fluid was forced during the days after the administration of the drug, but no sodium bicarbonate was given. The control group of 23 children were treated with 0.2 Gm. of sulfadiazine per kilogram of body weight for the first days, followed by 0.1 Gm. per kilogram of body weight daily in divided doses and continued until the temperature was normal for two days. The authors found that uncomplicated pneumococcic pneumonia in children seems to respond as promptly to a single dose of sulfadiazine as to continued doses of this drug. The temperature dropped to normal in from four to ninety-six hours, or an average of 38.4 hours, following the single dose, and in from six to one hundred hours, or an average of 40.1 hours, when a full course of sulfadiazine was given. No toxic manifestations appeared following the single dose treatment. It is simpler and less expensive, and it may decrease the risk of toxic manifestations and sensitization to the drug. Three patients with pneumonia complicated by otitis media did not respond to the single dose treatment. The single dose treatment is not recommended for hospitalized, serious or complicated cases of pneumonia, but as an expedient for ambulatory cases or occasions when proper care is lacking.

Kentucky Medical Journal, Bowling Green

42:153-190 (June) 1944

Thrombophlebitis and Pulmonary Embolism. A. W. Allen—p. 160.
Rh Factor and Erythroblastosis Fetalis. Louise G. Hutchins.—p. 165.
Rh Factor. W. M. German.—p. 167.
Treatment of Carcinoma of Prostate. L. Atherton.—p. 169.
Renal Pathology Following Use of Sulfa Drugs. E. S. Greenwood. —p. 174.
Treatment of Urologic Conditions Resulting from Administration of Sulfonamides. O. Grant.—p. 178.
Study of 46 Cases of Poliomyelitis. E. P. Scott and G. R. Rowntree. —p. 182.
Diabetic Gangrene of Nasal Septum and Diabetic Coma in a Woman 66 Years Old. F. G. Speidel.—p. 184.

Medical Annals of District of Columbia, Washington

13:167-212 (May) 1944

"Beyond the Call of Duty." A. A. Vandegrift.—p. 167.
Correctible Defects at Selective Service Age. L. G. Rowntree.—p. 170.
Pulmonary Embolism and Infarction: Clinical and Postmortem Study of 50 Cases. S. Katz and B. J. Walsh.—p. 178.
Role of Private Physician and of Voluntary Agency in Control of Tuberculosis. P. P. McCain.—p. 190.

Missouri State Medical Assn. Journal, St. Louis

41:91-108 (May) 1944

Study of Nephrosis. W. H. Graham.—p. 91.
Diaphragmatic Hernia in Infancy: Report of Successfully Operated Case. J. G. Probstein and J. Diamond.—p. 95.

41:109-130 (June) 1944

Control Factors in Surgery of Cancer Patients. E. D. Sugarbaker. —p. 112.
Committee on Postwar Planning: Preliminary Report and Plea. M. P. Neal.—p. 116.

Nebraska State Medical Journal, Lincoln

29:165-200 (June) 1944

President's Address. A. L. Cooper.—p. 169.
Medical Education of Today and Its Effect on the Future of Medicine. E. J. Carey.—p. 172.
Debt of a Graduate in Medicine. E. V. Allen.—p. 178.
I May Be Sued for Malpractice If . . .? R. W. Fouts.—p. 182.
In Case of Accident "Splint 'Em Where They Lie." J. E. M. Thomson. —p. 185.
Voluntary Nonprofit Prepayment Sickness Insurance. A. J. Offerman. —p. 187.

Oklahoma State Medical Assn. Jour., Oklahoma City

37:193-238 (May) 1944

*Clinical Observations in Use of Penicillin. E. R. Denny, P. L. Shallenberger and H. D. Pyle.—p. 193.
Cancer of Prostate. A. R. Sugg.—p. 206.
Congenital Defects of Sternum, with Report of a Case. J. F. Burton.—p. 210.

Clinical Observations in Use of Penicillin.—In accordance with a suggestion of the Surgeon General's Office, a board of medical officers consisting of men from the medical, surgical and orthopedic services and the hospital bacteriologist was appointed for the purpose of selecting patients for treatment with penicillin and for evaluating its effect. Denny and his collaborators found it most practicable to treat the majority of patients in a special penicillin ward. The drug is kept in the ward in refrigerators, the temperatures of which are maintained at approximately 4 C. Fresh solutions are made up each day with pyrogen free isotonic solution of sodium chloride. The intramuscular administration is the method of choice in most cases because of its simplicity. A technician can be trained to give the treatments, less supervision is required, and the majority of infections respond satisfactorily. For local application a solution containing 100 to 250 units of penicillin per cubic centimeter is prepared with isotonic solution of sodium chloride as a solvent. When practicable, wet dressings are applied to the wound and are overlayed with an impervious material. The authors analyze 276 cases treated by them. Penicillin appears to be highly effective in the treatment of sulfonamide resistant gonorrhea, as evidenced by the fact that 98.7 per cent of 243 patients were cured with 50,000 and/or 100,000 units. There was a satisfactory response to penicillin in all patients suffering from infections caused by streptococci of the beta and alpha types, and pneumonia caused by the pneumococcus. Infections due to Staphylococcus aureus responded satisfactorily in those whose lesions were superficial, in whom adequate drainage was instituted or in whom the disease was relatively acute, but in those in whom drainage was incomplete or in whom a foreign body or sequestrum existed the results have been unsatisfactory. No conclusion can be drawn from the authors' observations in the treatment of acute rheumatic fever in view of the fact that relatively small doses were used in 4 patients. Clinical and bacteriologic observations indicate that penicillin is highly effective in the treatment of Vincent's infection.

Public Health Reports, Washington, D. C.

59:609-636 (May 12) 1944

Organization of Medical and Sanitary Program, Alaska Highway Project. E. H. Carnes.—p. 609.
Pathologic Changes in Sheep Resulting from Exposure to Low Barometric Pressures. J. W. Miller.—p. 618.
Sickness Absenteeism Among Industrial Workers, Final Quarter of 1943, with Note on Occurrence of Respiratory Diseases, 1934-1943. W. M. Gafafer.—p. 620.

59:637-668 (May 19) 1944

Chemotherapy of Burns and Shock: VI. Standardized Hemorrhage in Mouse; VII. Therapy of Experimental Hemorrhage. H. Tabor, H. Kabat and S. M. Rosenthal.—p. 637.

59:669-700 (May 26) 1944

*Studies in Trichinosis: XVI. Epidemiologic Considerations Based on Examination for Trichinae of 5,313 Diaphragms from 189 Hospitals in 37 States and District of Columbia. W. H. Wright, L. Jacobs and A. C. Walton.—p. 669.

Epidemiologic Aspects of Trichinosis.—Wright and his associates reported in a previous communication the findings of trichinae in the examination of diaphragm material from 5,313 necropsies in various parts of the United States. Of these, 855, or 16.1 per cent, were positive for this parasite. They find no correlation between trichina infection and sex, civil or military status, past military service, occupation, mental hospitalization, urban or rural residence, or social-economic status. The 5,313 cases included 769 persons of foreign citizenship or whose names indicated foreign extraction, of whom 181, or 23.5 per cent, were infected. Persons in the German and Italian groups totaled 380, of whom 109, or 28.7 per cent, were infected. A comparison of these figures with an incidence of 15.6 per cent in 4,219 American Negroes and white persons of English-Scotch-Irish descent would seem to indicate that persons of foreign extraction are more frequently exposed to trichinosis. This applies only to persons in the German and Italian troops, since the infection rate in other foreigners was not significantly different than that for the group as a whole. Represented were 235 Jews, of whom only 5, or 2.1 per cent, were infected. Of the 855 positive cases 245, or 28.7 per cent, exhibited infections with live larvae, 142, or 16.6 per cent, infections with mixed live and dead larvae and 468, or 54.7 per cent, infections with dead larvae. There is evidence that death of the larvae may occur within a few years after infection. Within the continental limits of the United States exposure to trichinosis is nearly uniform in degree regardless of geographic or environmental factors. Control measures therefore must be enacted on a nationwide basis.

Radiology, Syracuse, N. Y.

42:319-424 (April) 1944

Kidney Tumors: Classification, Review of Symptoms, Methods of Diagnosis, Therapy and End Results. W. E. Howes.—p. 319.
Malignant Tumors of Kidney: Review of 117 Cases. L. C. Bixler, K. W. Stenstrom and C. D. Creevy.—p. 329.
Diagnostic Value of Pneumoperitoneum. J. R. Maxfield Jr. and A. J. McIlwain.—p. 346.
Responsibility of Roentgenologist in Wartime Duodenal Ulcer Problem. M. Feldman.—p. 356.
Primary Malignant Neoplasm of Shoulder Joint, with Report of Case. H. A. Olin.—p. 359.
Nomographic Aids in Calculating Radium Dosage for Plane and Point Sources. B. S. Wolf.—p. 368.
Roentgen Detection in Army General Hospital of Chronic Diseases Not Excluded by Induction Boards. L. M. Pascucci.—p. 375.
Value of Delayed Examination in Pyelography. E. C. Osgood.—p. 380.
Aortic Arch and Cardiac Mensuration. D. E. Ehrlich.—p. 382.
Training of X-Ray Technicians at School for Medical Department Enlisted Technicians. W. W. McCaw.—p. 384.
*Congenital Absence of Lung Diagnosed Before Death. E. R. Deweese and J. C. Howard Jr.—p. 389.

Congenital Absence of Lung.—Agenesis of the lung is a definite clinical entity. Its early recognition will give the patient a much better chance for life. Diagnosis may be made on the basis of x-ray examination, injection of iodized oil and bronchoscopy. Schneider has differentiated three main types of pulmonary agenesis. The first type is a true aplasia with no trace of lung, bronchus or vascular supply on the affected side. The second type is characterized by a small outpouching from the trachea, with rudimentary bronchus. In the third type the bronchus is fully formed but ends in a fleshy mass of areolar tissue of varying amount. The different types of pulmonary agenesis may be explained on an embryologic basis. The left lung seems to be absent more frequently than the right lung. The incidence of the condition is about the same in the two sexes. The authors report a case of pulmonary agenesis which represents the second one of this type of congenital defect seen at their hospital during the last six years. The patient was a boy aged 6 months. The admission diagnosis was atelectasis of the right upper lobe. Roentgenographic and bronchographic examination revealed that no air was entering the right lung, but the findings were considered not inconsistent with a true agenesia of the right lung. The child's condition became much worse and death occurred. Necropsy revealed no lung at all on the right side.

Review of Gastroenterology, New York

11:149-222 (May-June) 1944

Anomalies of Digestive Tract. W. Nimeh.—p. 165.
Gastroenteric Reflexes, Normal and Pathologic, as Noted by Means of Stimulation with Sodium Sulfate, with Special Reference to Postoperative Symptoms in Chronic Appendicitis. J. Carrere.—p. 169.
New Test for Gastric Function with 2-Bencil 4-5 Imidazoline. J. Nasio.—p. 174.
Primary Duodenal Diverticula: Review of Recent Literature; Report of Case with Severe Hemorrhage. L. L. Frank.—p. 179.

Tennessee State Medical Assn. Journal, Nashville

37:147-182 (May) 1944

Voluntary Nonprofit Prepayment for Health Care. J. R. Mannix.—p. 152.
Local Treatment of Burns. O. G. Nelson.—p. 159.

37:183-214 (June) 1944

Recent Progress in Industrial Health. C. M. Peterson.—p. 183.
Contribution of Medical Profession to War Effort. J. L. Cook.—p. 186.
Tube Feeding. O. S. Hauk.—p. 190.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Journal of Experimental Pathology, London

25:1-26 (Feb.) 1944

Distant Tumors Produced by 2-Amino- and 2-Acetyl-Amino-Fluorene. F. Bielschowsky.—p. 1.

Occurrence of A, B and O Blood Group Substances in Pseudomucinous Ovarian Cyst Fluids. W. T. J. Morgan and Ruth Van Heyningen. —p. 5.

*Serum Colloidal Gold Reaction as Liver Function Test. N. F. MacLagan.—p. 15.

Comparison Between Reactions of Acute Phase Serum with Pneumococcus C-Polysaccharide and with Pneumococcus Type 27. G. Löfström.—p. 21.

Serum Colloidal Gold Reaction as Liver Function Test.—MacLagan found that the serum colloidal gold reaction is greatly influenced by the reaction and the ionic strength of the medium. The technic has therefore been modified by the introduction of a buffer solution, which permits the test to be performed in a single tube in a reproducible manner without preliminary standardization of the gold sol. The conditions chosen give a final serum dilution of 1 in 60, a p_H of 7.8 and an ionic strength of 0.01. The results obtained in 200 jaundiced and 200 nonjaundiced patients suggests that the test is a valuable indicator of liver damage. The almost uniformly negative results in obstructive jaundice give it a particular value in distinguishing this condition from infective hepatitis or hepatic cirrhosis. The results in arsenical jaundice (40 per cent positive) were strikingly different from those in infective hepatitis (95 per cent positive), suggesting some essential pathologic difference in the two groups.

British Journal of Surgery, Bristol

31:313-428 (April) 1944

War Surgery in Africa. W. H. Ogilvie.—p. 313.

Mobile Neurosurgery in Warfare: Experiences in Eighth Army's Campaign in Cyrenaica, Tripolitania and Tunisia. K. Eden.—p. 324.

*Studies in Pathology of Human Immersion Foot. W. Blackwood. —p. 329.

Problems and Principles of Restoration of Limb Function Following Injury, as Demonstrated by Humeral Shaft Fractures. F. S. A. Doran.—p. 351.

Carcinoma of Ampulla of Vater: Successful Radical Resection. K. Watson.—p. 368.

Case of Sulfuric Acid Burns. G. W. Cashell, H. B. Shay, D. C. Bodenham.—p. 373.

*Fat Embolism in War Surgery. J. V. Wilson and C. V. Salisbury. —p. 384.

Adrenosympathetic Syndrome with Transposition of Viscera. L. R. Broster and R. C. McKeith.—p. 393.

Sarcoma of Stomach. A. E. Porritt, K. E. A. Hughes and R. J. C. Campbell.—p. 395.

Observations on Regeneration of Semilunar Cartilages in Man. I. S. Smillie.—p. 398.

Fracture Dislocation of Base of Fifth Metacarpal Bone. B. C. Murless.—p. 402.

Pathology of Human Immersion Foot.—Blackwood reports observations on 14 specimens of immersion foot studied at the Department of Pathology of the University of Edinburgh. The specimens varied in type from a digital nerve to a whole foot and leg, and they have varied also in the interval which has elapsed between the period of exposure and the removal of the specimen. All the material has come from severe cases with the result that gangrene and bacterial infection have often been present. The large arteries showed no severe narrowing. Slight intimal and medial fibrosis was sometimes present, also edema. The smaller arteries showed narrowing only immediately proximal to chronic infection. No significant changes were seen in the capillaries, but there were pericapillary foci of chronic inflammatory cells in the cases complicated at some time by infection and/or gangrene. Fibrous narrowing of small veins, with evidence of old hemorrhage into and around their walls, was seen either near gangrenous extremities, in chronically infected leg stumps or near an old amputation. The large veins showed significant narrowing due to patchy recanalized thrombus only when the leg stumps were chronically infected. Stasis of blood on the venous side, with diapedesis, thrombosis and intimal fibrosis, did occur, but such changes were restricted to areas close to gangrenous or chronically inflamed extremities. Involvement of muscle fibers increased peripherally. From four months onward the muscle picture was one of variation in fiber caliber, with relatively little fibrosis. These changes were indistinguishable from those due to denervation and were associated with degeneration of muscle nerves. In addition there were occasional small areas of replacement of peripheral muscle fibers by fibrous tissue. At twelve months there was evidence of reinnervation of proximally situated muscles in the lower limbs. At twenty-six months after exposure, restoration to normal had spread farther down the limb, but changes indistinguishable from prolonged denervation were still present. In all patients surviving exposure, some degree of nerve degeneration was present. In uninfected patients when bone was available for study there was new bone formation subperiosteally and around the haversian canals. This was evidence of repair of the initial osteoporosis, which is a clinical feature of early survivors. The microscopic studies on patients with immersion foot demonstrate that damage is done to all tissues of the extremity.

Fat Embolism in War Surgery.—Wilson and Salisbury think that a definition of fat embolism as a state in which globules of fat are present in the circulation of sufficient size to cause blockage of the intimate vascularities of various organs may be accepted in principle, though there is evidence that local action of the fat particles on the capillary walls may be a feature of the condition. Their study is based on 1,000 consecutive battle casualties admitted to the surgical wards of a military hospital. No attempt was made at selection; the only proviso made was that for patients who recovered the injury should have been serious enough to warrant their stay in hospital for at least a week. These patients suffered from all types of war injury, but 119 had fractures of the long bones only. There were 8 patients with clinical fat embolism among the 1,000 and 6 of the 8 died. The pathogenesis of this condition and the actual mechanism involved are not clear. There is no definite laboratory examination which can always be relied on for early diagnosis. Sputum examination is of doubtful value. Fat in the urine is diagnostic, but it appears rather late in the condition. Darkground illumination of the blood would appear to be the most helpful examination. The blood picture is important. The treatment of fat embolism is empirical. The authors suggest venesection if the blood pressure allows it, followed by intravenous administration either of whole blood or of dextrose in saline solution. Working on the fact that insulin may aid the liver to remove fat from the blood, the authors have used this and consider it helpful, although the results are by no means dramatic. Care must be taken not to increase the pulmonary edema. For the dyspnea and cyanosis the administration of oxygen is extremely helpful. Sedatives may be necessary in the irritative stage of cerebral embolism. When pneumonia develops, treatment is along the usual lines.

Journal of Hygiene, London

43:291-362 (April) 1944

Statistical Examination of Accuracy of Vitamin A Assays: An Analysis of Three Cooperative Experiments Designed to Ascertain Value of Conversion Factor for Transforming Spectrophotometric Values into International Units. J. O. Irwin.—p. 291.

*Sex Ratio of Pneumonia. Mortality. W. J. Martin.—p. 315.

An Atypical Neisseria Causing Meningitis. J. L. Edwards.—p. 328.

Studies in Immunization by Species Antigen: II. Presence of "Species Antigen" and of "Opposition Factor" in Bacteria Other Than Pneumococci. H. B. Day.—p. 330.

Revaccination as Measure of Immunity to Smallpox. E. S. Horgan and M. A. Haseeb.—p. 337.

Diphtheria in Glasgow 1934-1942. H. S. Carter.—p. 341.

Pressure Operated Safety Circuit for Use in High Vacuum Serum Drying Plants. F. B. Byrom.—p. 349.

Use of Antiseptic Sprays for Air Sterilization: Summary of Report to Medical Research Council. R. J. V. Pulvertaft.—p. 352.

*Epidemiology of Q Fever. E. H. Derrick.—p. 357.

Sex Ratio of Pneumonia Mortality.—According to Martin an excess of male over female mortality has been a feature of the respiratory diseases, particularly of pneumonia. He analyzes the average male mortality expressed as a percentage of the average female mortality from pneumonia for the fifteen

years from 1924 to 1938 for the areas of London, the county boroughs, urban and rural districts and for four age groups. A table shows that urbanization had little effect on the mortality sex ratio at the younger ages and only to a slight extent in the oldest age group, but at ages from 15 to 65 years there was, excluding London, a distinct progression with urbanization. In each age group the males experienced a higher mortality than the females, and the males were at a greater disadvantage during infancy than in childhood or old age, but the striking difference between the sexes occurred at ages of 15 to 65, when the males had a mortality twice as large as the females. The large mortality sex ratio found at ages 15 to 65 suggests that the differences between the mortality of the sexes may be caused by occupations with a high pneumonia risk. There is little evidence of an occupational risk for males; however, some occupations, such as furnace tending, involve a direct risk of pneumonia. The liability of these men to respiratory diseases was attributed by Vernon to the abrupt changes in the temperature to which the men were exposed by the conditions under which they worked, i. e. hot, heavy and exhausting spells of work alternated with periods of rest. Other occupations involve a more indirect risk; these include innkeepers, hotelkeepers, bartenders and makers of alcoholic drinks. The prognosis of pneumonia is affected by previous indulgence in alcohol, and the aforementioned occupations have a higher proportion of heavy drinkers than does the general population, and these occupations have a high mortality from pneumonia. A greater susceptibility among males than among females to infection or a greater power of recuperation possessed by females may be a possible explanation of the general excessive male mortality. During the working years of life a considerable part of the large male excess must be attributed to an indirect occupational risk, the general conditions of life that an occupation involves, rather than to the type of occupation.

Epidemiology of Q Fever.—According to Derrick investigations in Brisbane revealed that Q fever is a rickettsiosis and that it occurred also among farm workers and others. It was named Q fever and the causative organism Rickettsia burneti. In seven years 176 cases of Q fever have been diagnosed in Queensland. Nearly all the 129 patients who lived in Brisbane were associated with meat works. Most of the 47 country patients worked on dairy farms. Investigation of native animals, cattle and ticks has indicated in outline the natural history of Q fever. Several steps in this outline need confirmation, and much detail remains to be filled in. First there is a basic cycle of infection with the bandicoot and probably other bush animals as reservoir, and Haemaphysalis humerosa and probably Ixodes holocyclus as vector. A bush worker may interrupt this cycle and get Q fever from the attack of Ixodes holocyclus. Cattle become infected probably through Ixodes holocyclus and perhaps through other ticks. It is possible that there is a secondary cycle: cattle—Haemaphysalis bispinosa—cattle. Ticks on the cattle (Boophilus annulatus microplus or Haemaphysalis bispinosa) are probably the source of human infection. It is suggested that inhalation of tick feces is the likely mode of entry of Rickettsia burneti.

Journal of Royal Army Medical Corps, London

82:99-150 (March) 1944

Medical Aspects of Occupation of Captured Enemy Towns and Ports. W. L. Spencer-Cox.—p. 99.
Analysis of 422 Cases of Infection of Throat and Gums. T. Crawford. —p. 105.
Surgery in West Africa: Experiences in Military Hospital. W. M. Dennison and A. L. Dick.—p. 112.
Experiences of Battle Casualty at El Alamein. J. C. Bishop.—p. 125.
*Corneal Vascularity as Sign of Ariboflavinosis. J. G. Scott.—p. 133.

Corneal Vascularity as Sign of Ariboflavinosis.—Of 536 Europeans, according to Scott, 37 per cent had corneal vascularity. Of 1,700 Africans, 5 per cent presented corneal vascularity. Judged by perlèche, cheilosis and glossitis, the Africans had double the European numbers of ariboflavinosis. Corneal vascularity therefore cannot be taken as a guide to avitaminosis in the African. Of 136 Europeans who were examined by slit lamp, 70 took a course of riboflavin while 50 acted as controls. This therapeutic test was negative. The degree of vascularity fluctuates with or without riboflavin. Corneal vascularity cannot be accepted as a guide to avitaminosis in Europeans. All the Africans examined had a rim of pigment at the corneoscleral junction. It is possible that this rim of protective pigment explains the striking difference in African and European corneal vascularity.

Journal of Royal Naval Medical Service, London

30:1-64 (Jan.) 1944

*March Fracture. J. K. Salmon.—p. 1.
Beriberi: Description of Condition in Ratings of Straits Settlements Royal Naval Volunteer Reserve, and Commentary on Clinical Appearance and Diagnosis. E. L. Thomson.—p. 6.
Abnormal Reactions to Punishment. R. R. Prewer.—p. 13.
*Epidemic of Hepatitis. N. M. McArthur.—p. 18.
Secondary Hemorrhage. W. G. Gill.—p. 22.
Plague (Bubonic and Pneumonic) in Port Said. S. L. Townsend. —p. 25.
"White Man's Grave"—West Africa Yesterday and Today. S. Miles. —p. 30.
The Maine Goes to Sea. R. A. W. Ford.—p. 34.
Rehabilitation. F. G. Ward.—p. 37.
Radiologic Diagnosis of Pulmonary Tuberculosis. J. F. M. Campbell. —p. 45.
Rapid Method of Moving Helpless Patients Into Hospital-Ship Boats in Abandoning Ship. R. A. W. Ford.—p. 47.

March Fracture.—Salmon points out that diagnosis of march fracture may be missed because of absence of a history of direct trauma and the comparatively few physical signs. The fracture is most commonly seen in the third or fourth metatarsal bones. Always transverse, it occurs across the neck or distal end of the shaft and typically without displacement. The x-ray appearance is a "fine hairlike crack" and in consequence is easily missed. There is usually no history of direct trauma, more often a gradual onset of pain in the metatarsal region. Examination of the patient often reveals little apart from slight edema over the dorsum of the foot and tenderness over the metatarsal involved. The earliest x-ray sign is a slight raising or thickening of the periosteum around the neck or shaft. This is accompanied by all ill defined osteoporosis of the cortex. A fine transverse crack may be detected. The periosteal elevation becomes fusiform with an increasing density, forming the precallus stage. Callus formation then occurs, finally to be absorbed leaving a thickened cortex. If the patient is first examined during the periosteal reaction a mistaken diagnosis may result, the most important of which is a sarcoma, but in the absence of cortical disturbance subperiosteal spiculation and further x-ray investigation should exclude this. March fracture must also be differentiated from Köhler's disease and from syphilitic periostitis. The author saw 5 cases of march fracture at a naval hospital, and of these 2 are described. The great importance of the x-ray investigation of patients complaining of slight pain and swelling over the dorsum of the foot is stressed. Further films should be taken during the following fortnight in the absence of positive findings in the first. Treatment is that of any other fracture, namely immobilization and rest.

Epidemic of Hepatitis.—McArthur reviews 46 cases of hepatitis which occurred among the personnel of a hospital ship numbering 244. There was a hospital staff of 110 and a ship's staff of 134. There were 45 cases of epidemic hepatitis among the hospital staff and only 1 among the ship's staff. All patients had received yellow fever vaccine on the same day, and jaundice appeared thirteen to twenty-three weeks later. There was a remarkable uniformity in the mode of onset. The symptoms were those usually associated with so-called catarrhal jaundice. There were no fatal cases, but debility was severe. Laboratory investigations in the more severe cases revealed a secondary anemia and hyaline and granular casts in the urine. A vaccine contaminated by the virus of epidemic hepatitis seems the most probable source of the epidemic. Certain of the cases may have been the result of contact infection, as it is otherwise difficult to explain the selective way in which the hospital staff was affected.

Lancet, London

1:489-522 (April 15) 1944

*Posthemorrhagic Fainting: Study by Cardiac Output and Forearm Flow. H. Barcroft, O. G. Edholm, J. McMichael and E. P. Sharpey-Schafer.—p. 489.
Poliomyelitis: Studies on Inciting Agent and Specific Serum Treatment. E. C. Rosenow.—p. 491.
*Vitamin K as Prophylactic in 13,000 Infants. J. Lehmann.—p. 493.
Gingival Disease in Gibraltar Evacuee Children. J. D. King and A. B. Francklyn.—p. 495.
Megalocytic Anemia as Sequel to Malaria. S. F. Seelig and J. R. Hemming.—p. 498.
Phonoelectrocardioscopy. G. E. Donovan.—p. 500.
Case of Contracted Bladder. S. I. Levy and J. S. Horn.—p. 501.
Three and a Half Years' Treatment with Sulfapyridine: In case of Dermatitis Herpetiformis. B. Barling.—p. 503.

Cardiac Output and Forearm Flow in Posthemorrhagic Fainting.—Barcroft and his associates think that vasovagal fainting reactions with acute fall of blood pressure and slow pulse demand detailed study because they constitute one manifestation of hemorrhagic or oligemic shock. They become increasingly frequent as hemorrhage increases in magnitude. Fainting occurs in 3.8 per cent of donors bled 440 cc., and the incidence rises to 8.5 per cent when the bleeding is increased to 540 cc. Studies of the effects of larger venesections on normal male volunteers show that of those bled 800 to 1,000 cc. 11 out of 28 fainted, and of those bled 1,000 to 1,200 cc. 15 out of 29 fainted. Some authors have ascribed fainting to lack of blood supply to the brain, others to vasodilatation in the peripheral vascular system and to bradycardia, a combination to which the term vasovagal syndrome was applied. The authors report studies on healthy young male volunteers. Cardiac output by a direct Fick method and mean right auricular pressure were measured by cardiac catheterization. Forearm blood flow was measured with the Lewis and Grant plethysmograph, the arm being immersed in a water bath at 35 C. When cardiac output and arterial pressure are known, an estimate of the resistance to flow imposed by the peripheral arterioles may be made. During fainting after hemorrhage cardiac output and right auricular pressure are often substantially unchanged. The acute fall in blood pressure cannot be explained by bradycardia and decreased cardiac output; it is due to peripheral vasodilatation. Forearm blood flow is approximately doubled; since the blood pressure is about halved, this indicates pronounced vasodilatation. The vasodilatation cannot be in the skin, which is pale; it is in the arterioles of the underlying muscle. If vasodilatation of the same order occurred throughout the body musculature there would be a considerable drop in the blood pressure, possibly great enough to explain the fall in fainting. The vasodilatation is mediated by vasomotor nerves.

Vitamin K as Prophylactic in 13,000 Infants.—According to Lehmann, synthetic analogues of vitamin K appeared on the Scandinavian market in 1940 and prophylactic treatment of newborn infants was then started. He investigated the physiologic hypoprothrombinemia in 90 newborn infants by daily determinations during the first week after birth. For this purpose he used a micro modification of Quick's method. Forty of the 90 infants in which determinations were made belonged to the summer series, that is, they were born during July and August. The other 50 infants were spring births (March and April). It was found that during spring low prothrombin values were more common than in summer. The minimal but optimal dose of a vitamin K analogue for prophylactic treatment of newborn infants after birth was found to be 0.5 to 1 mg. and was as effective when given by mouth as by injection. A comparison of deaths from bleeding in 13,250 full term infants receiving vitamin K analogue with 17,740 untreated cases showed that 1.6 per thousand could be saved by the treatment and that general prophylaxis can be recommended, since the cost is low. Hemorrhagic disease of the newborn was found to include all forms of bleeding, and especially intracranial bleeding.

Quarterly Journal of Medicine, Oxford

13:1-36 (Jan.) 1944

Myasthenia Gravis: Consideration of Its Causation in Study of 14 Cases. A. Wilson and H. B. Stoner.—p. 1.
Serum-Iron in Health and Disease. Joan F. Powell.—p. 19.
Loss of Weight in Obese Patients on Submaintenance Diets and Effect of Variation in Ratio of Carbohydrate to Fat in Diet. A. B. Anderson.—p. 27.

Transactions Royal Soc. Trop. Med. and Hyg., London

37: 287-346 (March) 1944

*Pigment Metabolism and Renal Failure in Acute Sulfonamide Hemolysis Resembling Blackwater Fever. H. Foy, J. Gluckman and A. Kondi.—p. 303.
Technic and Interpretation of Weil-Felix Test in Typhus Fever. A. Felix.—p. 321.
Note on Preparation of Suspensions for Weil-Felix Test. R. F. Bridges.—p. 343.

Sulfonamide Hemolysis Resembling Blackwater Fever.—Foy and his associates show that the intravascular hemolyses in blackwater fever, incompatible transfusions, hemolytic jaundice and hemolysis from various drugs resemble one another. They report a case in which benzyl sulfanilamide had been given. Complete quantitative pigment estimations in blood and urine were made and correlated so that a comparison between the pigment metabolism in this condition, blackwater fever, and the other intravascular hemolyses was possible, bringing out the resemblances and differences between them. Intracorpuscular methemoglobin occurs after sulfonamides, plasmochin and acetanilid but does not occur in blackwater fever. Oxyhemoglobin, methemalbumin and hemobilirubin are common to all the intravascular hemolyses. It appears that p-aminophenol or one of its derivatives is responsible for the methemoglobinemia after aniline and acetanilid; it seems uncertain whether or not similar metabolites are responsible in the case of sulfonamides and plasmochin. In the case described there existed an acute massive intravascular hemolysis accompanied by the presence of plasma oxyhemoglobin, methemalbumin and hemobilirubin, as well as intracorpuscular methemoglobin and a profound fall in the red cell count. Urinary methemoglobin may be present in the intravascular hemolyses, but its presence in the urine is not related to plasma methemalbumin or intracorpuscular methemoglobin; nor is its formation entirely dependent on urinary p_H or ionic concentration. Both oxyhemoglobin and methemoglobin were found in the urine. There was an almost complete anuria that was not associated with blockage of the renal tubules with precipitated products of hemoglobin. There were, however, changes in both the tubules and the glomeruli, such as are characteristic in blackwater fever and incompatible transfusions. It is suggested that the anuria and azotemia are secondary to more fundamental changes that occur in the blood stream and which lead to upsets in glomerular filtration, tubular reabsorption, anuria and azotemia, and that blockage is a secondary phenomenon. In the present case there was a great difference in the microscopic appearance of the kidney tubules and glomeruli in the paraffin and frozen material. It is felt that the distortion brought about by the dehydration consequent on the paraffin method makes this technic unsatisfactory for correctly assessing the changes that take place in these delicate structures in the anuric condition. The great increase in the osmotic resistance of the red cells to saline solution and to lysolecithin was not related to changes in the cell volumes, thicknesses, diameters or ratios, and the Price-Jones curve was within normal range. The authors feel that changes in the environment of the cells, perhaps in the nature of circulating hemolysins, are more fundamental than physical changes in red cell structure.

Schweizerische medizinische Wochenschrift, Basel

73:497-520 (April 24) 1943. **Partial Index**

Medical Survey of Accidental Injuries and Roentgenographic Studies. F. Lang.—p. 497.
*Character and Diagnosis of Infantile Rickets. E. Wieland.—p. 500.
Contribution to Studies of Ventriculometry. A. Melley.—p. 506.
Cosmos and Man. E. Jenny.—p. 511.

Infantile Rickets.—Wieland's experience in the pediatric clinic in Basel suggests that craniotabes in the form of supraoccipital softening not only is pathognomonic of rickets but also represents the primary positive clinical sign of rickets. Isolated localizations of rickets in the skeleton may continue for a long time and may disappear temporarily or permanently since rickets is a chronic, remittent disorder of metabolism. That is why supraoccipital softening of the cranium may be observed in healthy infants. This symptom may be overlooked

for the same reason and its nosologic importance may be misunderstood. For many years incipient craniotabes had been mistaken for congenital defect of the cranium culminating in a soft cranium. All congenital disturbances of ossification of the cranium prior to and after birth subside spontaneously and become normal within the first four to six weeks after birth. Any recent supraoccipital softening or any increase in congenital supraoccipital softening in infants regardless of the interval between its occurrence and birth is rickety in character and requires specific therapy. Recovery will take place on administration of vitamin D (irradiated ergosterol or Vi-De) in any instance of uncomplicated rickets. Massive doses of vitamin D for a short time are not superior to small doses for a longer period but may be preferred in rapidly advancing cases, in those complicated by pneumonia and in cases of premature birth.

73:737-760 (June 5) 1943

Surgery of Cancer of Large Intestine, Except for Cancer of the Rectum. O. Häuptli.—p. 737.
Combined Metrazol-Epinephrine Shock Therapy of Epilepsy. A. Juba and L. Fórizs.—p. 741.
*Biologic Reasons for Ineffectiveness of Sulfonamide Therapy in Severely Infected Wounds. H. Paschoud.—p. 743.
Symptomatic and Causal Treatment of Hay Fever and Hypotension Allergy. J. Strebel.—p. 746.

Ineffectiveness of Sulfonamide Therapy for Severely Infected Wounds.—Paschoud states that local sulfonamide therapy by application of dusting powder, crystals or solution in severely infected or contaminated wounds failed since diffuse phlegmons, erysipelas and gas gangrene present a continuous threat. Three factors are responsible for this failure: 1. Any drying effect with tendency of diminishing the secretion of the infected wound, instead of increasing its lymphorrhea must be deleterious. 2. The determination of the p_H at intervals of two hours in 11 cases revealed the ineffectiveness of the local application of sulfonamide dusting powders in the control of the acidosis which develops in the deep recesses of the purulent layer of the wound. 3. It is Paschoud's experience that the normal course of an infected wound may be favorably influenced by a surface temperature up to 45 degrees (by contact with the potentiometer). Potentiometric determinations in those 11 cases demonstrated that the local application of sulfonamides does not prevent a progressive local drop in temperature.

73:761-792 (June 12) 1943. **Partial Index**

*Primary Group Infection with Tuberculosis in Military and Civil Life. W. Löffler and F. Zwingli.—p. 761.
Tuberculosis and Army in Active Military Service in 1939 and in the Following Years. E. Uehlinger.—p. 769.
Tuberculosis and Army in Active Military Service in 1939 and in the Following Years. Morgenthaler.—p. 774.
Results of Systematic Roentgenologic Examination of Recruits in Army Unit After Their Induction in 1942. C. Frei.—p. 778.
Epidemiology of Tuberculosis in a Small Village in the Jura of Vaud. C. Bezençon, G. Cornu, H. Pache, P. Rochat and E. Urech.—p. 782.
Prevention of Tuberculosis. E. Bachmann.—p. 787.
Problems of Military Insurance. E. Bachmann, M. Kartagener and W. Löffler.—p. 789.

Primary Group Infection with Tuberculosis.—Löffler and Zwingli report two endemics of primary group infections with tuberculosis. The person whose primary infection indicates a source of infection is referred to as the indicator. The person who transmits the infection is a donor and all the other members of the same group with tuberculosis are receptors, each of whom may have likewise served as an indicator. One of the groups consisted of 13 adults in a military unit. The donor was a man aged 24 with pulmonary cavernous tuberculosis. Primary tuberculosis developed within two years in these cases from contact with the donor. The receptors probably acted as donors for some of the cases. Open tuberculosis was demonstrated on examination of some of the receptors, and chain infection was caused by the donor and transmitted by some of the receptors. A primary complex was revealed in 10 of the 13 cases. Three of them presented the picture of phthisis with primary focus. Associated pleuritis was demonstrated in 10. The pleuritis in 9 resulted from contact at the same time as the primary complex or within a short time after its development. Fatal hematogenous infection secondary to the primary complex occurred in only 1. The second group consisted of 9 persons, 3 adults and 6 children between the ages of 4 and 14 years living in the same household. The severe course of primary tuberculosis in 6 of these cases within a closed community suggested that the donor was to be found within the household. The examination of the members of the household demonstrated as donor a man aged 48 with tuberculosis of both upper lobes, with a large subclavicular cavity on the right side and aspiration foci in both inferior lobes. The sputum was positive for bacilli on repeated examinations. The infectivity of tuberculosis is emphasized and immunization experiments with BCG vaccine are suggested. The majority of the cases presented primary infections which were demonstrated on examination in the postprimary stage. Exogenic infection, therefore, should be considered in each case. The source should be sought not only after the demonstration of the last case but immediately after that of the first case in order to prevent further spread of the disease.

73:793-816 (June 19) 1943. **Partial Index**

Critics and Casuistics of Roentgenologic Examinations in the Army. H. H. Weber.—p. 793.
*Coronary Sclerosis in Youths. A. von Albertini.—p. 796.
Feasibility and Technic of Sulfonamide Therapy by Rectal Route. G. Rieben.—p. 797.
Expediency of Electrocardiography in Relation to Other Methods of Physical Examination. O. Merkelbach.—p. 801.
Symptomatic and Causal Treatment of Hay Fever and Hypotension Allergy. J. Strebel.—p. 805.

Coronary Sclerosis in Youths.—Arteriosclerosis of the type of isolated malignant stenotic sclerosis occurs in young persons. The specific inflammatory character of coronary stenosis resembles that of thromboangiitis obliterans (von Winiwarter-Buerger's disease). There is a consensus that the latter represents an inflammatory process. The resemblances of the two diseases are demonstrable by microscopic studies and by the clinical and anatomic sequences of coronary insufficiency, angina pectoris and myocardial infarcts, on the one hand and intermittent claudication, circulatory and trophic disturbances of the extremities, necrosis and gangrene on the other. Both diseases occur almost exclusively in men. There is also conformity with regard to age. Coronary stenosis represents Buerger's disease of the coronary arteries. Secondary arteriosclerosis occurs at a later stage of both conditions. This condition develops from the scar that was left in the wall of the vessel by the primary inflammation. Cholesterol is not the etiologic factor. Factors causing mild inflammation with little destruction of tissue play a part in the causation of Buerger's disease. The tendency toward recovery is predominant. The patient suffers chiefly from cicatrization. The concept of focal infection of mild virulence is suggested.

Semana Médica, Buenos Aires

51:801-852 (April 20) 1944. **Partial Index**

*Transfusion of Suspensions of Blood Globules. A. M. Romero Alvarez.—p. 805.
Pregnancy and Atelectasis. J. Melfi and A. Molina.—p. 812.

Transfusion of Suspension of Blood Corpuscles.—Romero Alvarez prepares corpuscle suspensions as follows: Five hundred cc. of blood is placed in a flask and left in the ice box for twenty-four or forty-eight hours, after which the plasma is removed. A volume of a 5.4 per cent of dextrose solution in isotonic solution of sodium chloride equal to that of the removed plasma is added. The solution is then ready for use. It can be stored for from one to four days. The indications for its use are posthemorrhagic anemia and anemia of cardiac insufficiency. Hemoconcentration, shock, burns and hypoproteinemia constitute contraindications. The author transfused suspensions of blood corpuscles to 36 patients with posthemorrhagic anemia. The number of transfusions varied from one to eighteen. The amount for each transfusion varied from 100 to 500 cc. Corpuscle suspensions are tolerated better than total blood, for which they are a good substitute. The importance of administering cell suspensions to the wounded in war, as well as to the victims of various catastrophes among civilians, is emphasized.

Book Notices

Allergy in Practice. By Samuel M. Feinberg, M.D., Associate Professor of Medicine and Chief of the Division of Allergy, Northwestern University Medical School, Chicago. With the collaboration of Oren C. Durham, Chief Botanist, Abbott Laboratories. Cloth. Price, $8. Pp. 798, with 36 illustrations. Chicago: Year Book Publishers, Inc., 1944.

The author has succeeded in writing a book in simple language, easy to read and to understand. The arrangement of the subject matter, using normal type in the presentation of the generally accepted material and smaller type for the more controversial aspects, is to be commended. The chapter on allergy to fungi is complete and includes Dr. Feinberg's special studies in this field. The chapter on pollen and pollen allergy was written by Oren C. Durham, whose many years of experience with botanic surveys in various sections of the United States makes his contribution a valuable addition to the book. Every section of the country is mapped botanically, a great help to practitioners in their respective localities. The major portion of the book is, as expected, devoted to the diagnosis and treatment of hay fever and asthma. This phase of the subject is fully covered. However, the other allergies are not neglected, fully one fifth of the book concerning itself with allergic coryza, urticaria and angioneurotic edema, the dermatoses, migraine and gastrointestinal allergy. Diagnosis and differential diagnosis are sufficiently detailed, and the treatment outlined is very practical. Each chapter is summarized. The bibliography is fairly complete. The use of the term adrenalin instead of the more appropriate epinephrine hydrochloride is an oversight. All in all, this book may be used profitably by both the beginner and the specialist in allergy and is recommended highly.

Polinosis. Por Leopoldo Herraiz Ballestero, doctor en medicina, y Juan Victor Monticelli, doctor en ciencias naturales. Prólogo del Profesor Carlos Jiménez Díaz. Paper. Pp. 227, with 2 illustrations. Buenos Aires: Libreria Hachette S. A., Palacio del Libro, 1943.

The authors, a physician and a botanist, present their closely integrated efforts over a period of four years in digesting the literature on pollen allergy, particularly from North and South America, and in carrying out comprehensive field, atmospheric and clinical pollen research. The book is not offered as a monograph on pollen disease but as a general preliminary study of the local Argentine problem, which will be followed shortly by a long series of articles which are listed by title in the bibliography. Emphasis is placed on the basic importance of recognition of the local qualitative and quantitative differences in the exposure of sensitive persons to pollens, and the authors strongly advocate the method of parallel clinical evaluation of pollen species while the seasonal and geographic incidence of these species is being determined.

The first half of the book is devoted to the anemophilous flora and air borne pollen of eight of the most populous provinces and territories of central Argentina as compared with similar data from other parts of the world. Three floral zones are mapped. Two of these are made by dividing the pampas region into an eastern area where rainfall is more abundant and a western area of scant rainfall. The Andean zone is a narrow strip between the dry pampas and the continental divide. Daily tests of atmospheric pollen concentration have been carried out in eleven cities over a three year period. The botanic data are embodied in numerous tables supplemented with condensed comments.

The second half of the book covers the results of clinical work in Argentina and stresses the regional characteristics of pollinosis as related to the botanic studies already made. In matters of skin testing and preseasonal, coseasonal and perennial treatment the technic described is much the same as that followed by American authors, but the stock combinations of pollen extract described in the section entitled "Desensibilización Específica" would hardly meet the approval of allergists in this country.

The practical value of this book to physicians of the United States and Canada is obviously limited by the relatively small number of allergic persons who change their residence from North America to Argentina or vice versa.

Homicide Investigation: Practical Information for Coroners, Police Officers, and Other Investigators. By LeMoyne Snyder, Medicolegal Director, Michigan State Police. With chapters by Captain Harold Mulbar, Chief of the Identification Bureau of the Michigan State Police, Charles M. Wilson, Director, Chicago Police Scientific Crime Detection Laboratory, and C. W. Muehlberger, Director, Michigan Crime Detection Laboratory. Cloth. Price, $5. Pp. 287, with 116 illustrations. Springfield, Illinois & Baltimore: Charles C Thomas, 1944.

The object of this book is to aid policemen, coroners and other officials in the investigation of deaths from unnatural causes. Special and detailed attention is given to the proper examination where and when the dead body is first found. Information of essential significance may be lost and the solution of vital problems prevented if this first examination is not done in the right way. The language is suitable, and the illustrations are instructive and realistic. The book will be of great value to all who must investigate apparently violent deaths, including practitioners who may be called on to make examinations in such cases. "Never touch, change or alter anything until identified, measured and photographed. Remember that when a body or an article has been moved it can never be restored to its original position." This is the golden rule for investigation in cases of suspected homicide, but the principle has wide application.

Paralisis infantil en Colombia. Por Luis Betancur Arango. Tesis de grado presentado a la Escuela de medicina para optar el titulo de doctor en medicina y cirugía, Universidad de Antioquia, Facultad de medicina y ciencias naturales. Paper. Pp. 138. Medellin, 1942.

Sporadic epidemics of subacute but typical poliomyelitis have been observed during the last twenty-five years in Colombia. Epidemic outbreaks occurred in Colombia at the same time at which epidemics occurred in several other countries. An epidemic among children under the age of 12 years was observed in the departments of Cauca, Valle del Cauca, Antioquía and Santander del Sur between October 1939 and August 1941. The patients in the department of Valle del Cauca acquired the disease from contagion during their stay in the department of Cauca. The author points out the importance of passing national laws for control of the disease. The therapy used in the 1939 and 1941 epidemics consisted of a daily dose of potassium chlorate by the mouth for two or three consecutive weeks. The patients had also 5 cc. of antistreptococcic serum daily up to a total dose of 20 cc. and a dose of 5 mg. of vitamin B every three days up to a total of 25 mg. The treatment had no effect on the course of the disease.

A Catalogue of the Medieval and Renaissance Manuscripts and Incunabula in the Boston Medical Library. Compiled by James F. Ballard, Director, Boston Medical Library. Cloth. Privately printed. Pp. 246. Menasha: George Banta Publishing Company, 1944.

The growth of the collection in the Boston Medical Library of incunabula and manuscripts is described in the introduction by Henry R. Viets, librarian. The compiler of the catalogue, James R. Ballard, has just completed fifty years of service to the library. He has had "a lifelong interest in manuscripts and the early printed medical books." Mr. Ballard lists 674 incunabula and 52 manuscripts. The list appears to include some edition or other of nearly every book of medical interest published before 1501. Scholars, librarians and bibliographers will appreciate the appended indexes of subjects, names, manuscripts, printers, publishers and patrons as well as the concordances to the lists of incunabula by Stillwell, Klebs and Osler. The illustrations are of singular interest. Special congratulations are extended to the Boston Medical Library and to Mr. Ballard on this contribution to bibliographic scholarship.

Elimination Diets and the Patient's Allergies: A Handbook of Allergy. By Albert H. Rowe, M.D., Consultant in Allergic Diseases, Alameda County Hospital, Oakland, California. Second edition. Cloth. Price, $3.50. Pp. 256. Philadelphia: Lea & Febiger, 1944.

The author states in the preface that the purpose of this book is twofold: "first to emphasize the importance of food allergy and, second, to discuss the other causes of clinical allergy with present day methods for their diagnosis and control." The second of these stated purposes is taken up in the first hundred and fifty pages of this book. The work is poorly done. The general physician without special training in allergy would have a confusing and incomplete picture of the allergic conditions and their methods of diagnosis from this part of the

book. The physician with only a limited but guided experience in allergy would have no need for the superficial remarks on many subjects contained in this first half of the book.

To clarify this statement are the following: Only three pages are given to contact dermatitis, its causes and methods of diagnosis; the entire subject of "sensitization" covers only one page; injectants, including serum sickness, drug allergy and vaccines, two pages; physical allergy, a brief paragraph; bronchial allergy and allergic bronchitis, eight pages; seasonal and perennial hay fever is treated in three pages. In a book with this title, the author might well have limited himself to a presentation of the principles of allergy in one hundred pages and presented the rest of his limited subject in the additional hundred pages.

The second part of this book, as in the first edition, is devoted to a thorough presentation of many useful elimination diets to fit a variety of diagnostic needs, together with sample menus and many useful and practical recipes. Additional recipes, information regarding various food components in mixed food preparations and much other useful information are contained in a loosely organized fashion in the final fifty pages of the book. The second part contains excellent material and much practical information for the reader who is able to organize such data.

Principles and Practice of Aviation Medicine. By Harry G. Armstrong, M.D., F.A.C.P., Colonel, Medical Corps, United States Army. Second edition. Cloth. Price, $6.50. Pp. 514, with 87 illustrations. Baltimore: William Wood & Company, 1943.

The second edition of this now universally accepted textbook on aviation medicine has no change in the purpose, scope or arrangement of the subject matter from that in the first edition, which has been reprinted four times. Colonel Armstrong is recognized as an authority on aviation medicine. He has been largely responsible for keeping development in aviation medicine concurrent with development in aviation industry. This edition will undoubtedly increase the widespread interest in aviation medicine in the United States and abroad. Information has been added on the effects of centrifugal force and on the emotional reactions to flight. The importance of taking oxygen at altitudes as low as 5,000 feet at night in order to avoid reduction of night vision is stressed, and diagrams of the correct and incorrect manners of looking at objects in dim illumination are presented. The main sections of the book are those that deal with the selection and care of the flier, physical factors in flight, anoxia in aviation, altitude sickness, mechanical effects of decreased atmospheric pressure, including aeroembolism and ear distress, pressure cabins, speed and acceleration and emotional reactions to flight. Naturally, a considerable portion of recent work in aviation medicine is classified as confidential and will not be available for publication until after the war; however, the inclusion of the unrestricted information available and the revision of several chapters, with addition of a number of illustrations and tables, are sufficient to make it mandatory for all persons interested in aviation medicine to read this book carefully.

Occupational Lead Exposure and Lead Poisoning. A Report Prepared by the Committee on Lead Poisoning of the Industrial Hygiene Section of the American Public Health Association. Paper. Price, 75 cents. Pp. 67. New York: American Public Health Association, 1943.

For some time there has been misconception of the etiologic factors, diagnosis, control and treatment of lead poisoning, as the result of enthusiastic publication of isolated procedures. This committee report is a practical authoritative statement on occupational lead exposure and poisoning which will clarify the situation. It is divided into five parts:

1. The recognition of hazardous lead exposures. This section covers the occurrence of lead poisoning in industry and the recognition and measurement of the exposure.

2. Safe limits of occupational lead exposure. This includes safe limits as shown by air analysis and clinical tests of blood and urine of workmen exposed.

3. Control of occupational lead exposure. This is a description of control by engineering features and the steps required in medical supervision of workers exposed to lead.

4. Occupational lead poisoning. A rather detailed description is given of the diagnostic procedure plus the management and treatment of lead poisoning.

5. Appendix and classified bibliography. The committee has not attempted to discuss completely all controversial points but has included this comprehensive bibliography, which gives the reader an opportunity to refer to any source material on specific points.

Introduction to Exceptional Children. By Harry J. Baker, Ph.D., Director, Psychological Clinic, Detroit Public Schools. Cloth. Price, $3.50. Pp. 496, with illustrations. New York: Macmillan Company, 1944.

By "exceptional children" the author means not only the physically or mentally handicapped but also those in the outer ranges of normal, such as the excessively tall, unusually strong or specially gifted. Part I of the book correlates the education of the exceptional child with the purposes of all education, namely training for "self realization," "human relationships," "economic efficiency" and "civic responsibility." Part II is devoted to the problems of children with visual, auditory, lingual and orthopedic defects. Part III considers the subnormal and the intellectually superior. Part IV deals with neurotic behavior abnormalities, and the following two sections again take up the general problems of the educationally retarded and the difficult child. Obviously, so great a variety of topics can be dealt with only superficially in a single book. Unfortunately too, for a volume intended as a textbook the style is frequently slipshod (p. 71: "Louis Braille . . . lost his eyesight with a knife at the age of 5 years while imitating his father, who was a saddler by trade") and too many careless statements are made (p. 51: "Guy de Maupassant . . . had diplopia due to paralysis of the extraocular muscles, and his death resulted from the general paresis caused by it"). Nevertheless, the material is well organized, and certain sections such as those on visual defects are clear and informative. Behavior is approached dynamically and in relation to physical, social, economic and other factors as well as purely pedagogic influences. The book should serve well as an introductory textbook for students of elementary education; perhaps later revisions and additions will expand its usefulness to social workers, psychologists and physicians.

Virus Diseases in Man, Animal and Plant. By Gustav Seiffert. A Survey and Reports Covering the Major Research Work Done During the Last Decade. [Translation by Marion Lee Taylor, Ph.D.]. Cloth. Price, $5. Pp. 332, with 7 illustrations. New York: Philosophical Library, Inc., 1944.

In 1938 this book appeared in its original German edition. In its 221 pages it filled a definite need for a concise digest of the general characteristics of viruses and specific consideration of the different diseases. A brief chapter on methods pointed out the basic technics. This book has now been published as a translation into English with the added endorsement that it is published on recommendation of the National Research Council. No attempt has been made to produce a new edition revised so as to include studies since 1938. Probably the present volume will serve as a source book for reference. It is well annotated. The English of the translation is, however, unbelievably awkward. Much of the German terminology and construction are preserved to the point that whole sections are ridiculous. There are numerous mistakes in spelling, and the proof reading has been badly done. It is shameful that a book of such inherent value should have been so mistreated.

Laboratory Methods of the United States Army. Edited by James Stevens Simmons, B.S., M.D., Ph.D., Brigadier General, United States Army, and Cleon J. Gentzkow, M.D., Ph.D., Colonel, Medical Corps, United States Army. Approved by the Surgeon General of the United States Army. Fifth edition. Fabrikoid. Price, $7.50. Pp. 823, with 111 illustrations. Philadelphia: Lea & Febiger, 1944.

The fifth edition of this well established work on laboratory technic indicates further progress in a book that has had a long and enviable record. The first edition appeared during the first world war, and other editions have been issued from time to time since that date. The present volume represents a composite work in which many distinguished investigators have cooperated. Every phase of clinical pathology is covered. The directions are explicit, the illustrations, particularly those on the distribution of tropical disease, most informative. References to the periodical literature which accompany the various chapters indicate that the work is quite up to date.

Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

HYPERSENSITIVITY TO SULFONAMIDE

To the Editor:—**I have been using a combination of powdered sulfanilamide and sulfathiazole for nasal insufflation in the treatment of head colds and sinus conditions. Is there any danger from prolonged therapy? What are the possibilities of sensitization to the sulfonamides? What tests determine whether or not a patient is sensitive to sulfonamides prior to their internal administration? In the event of sensitivity how can a patient be desensitized in order that the drug may be administered? Does sensitization eventually disappear if the patient abstains from using the drug over a period of time?**

M.D., New York.

ANSWER.—In discussing the effect of topically applied sulfonamides on human tissues, a distinction must be made between reactions resulting from toxicity of the compounds and a true type of induced hypersensitivity. This distinction is not too apparent at times. There is danger that a localized and, more rarely, a generalized type of hypersensitivity to sulfanilamide, and more particularly to sulfathiazole, may result from prolonged nasal insufflation of these compounds. Other than these possibilities there does not appear to be any danger, although some authorities are opposed to the use of solutions of sodium sulfathiazole for such purposes because of the possibility of producing tissue necrosis. Leftwich has recently proposed the thesis that hypersensitivity to the sulfonamides is an allergic reaction similar to serum sickness (An Intradermal Test for Recognition of Hypersensitivity to Sulfonamide Drugs, *Bull. Johns Hopkins Hosp.* **74**:26 [Jan.] 1944). Therefore, hypersensitivity to the sulfonamides may be detected by injecting intradermally serum which is obtained from a patient who is receiving a sulfonamide in doses so that a serum level of 2 mg. or more per cubic centimeter is present. An immediate type of reaction will be obtained in the patient who is hypersensitive to the drug. Before such a test can be accepted by the profession, confirmation of this work is necessary. A more commonly used procedure in patients suspected of being sensitive is to administer 0.5 Gm. of the drug by mouth and keep the patient under observation for ten to twelve hours. Patients who are sensitive to the compound will exhibit such reactions as fever, skin eruptions and nausea and vomiting. In the event that a patient does exhibit signs of sensitivity to one sulfonamide, it would be more practical to try another sulfonamide. While desensitization to a sulfonamide has been attempted, it is a time consuming and dangerous procedure. This has been accomplished, according to some reports, by the oral administration of a small dose of the drug, and then increasing the doses gradually. In general, real hypersensitivity to a particular sulfonamide has been shown to persist for as long as two to three years.

MANAGEMENT OF PATIENTS WITH AURICULAR FIBRILLATION AND CONGESTIVE FAILURE

To the Editor:—**A patient has chronic bronchial asthma, is 63 years old and has developed congestive heart failure. His pulse was rapid but regular until he was fully digitalized; then his heart began fibrillating, but his signs of congestion began to improve. On discontinuing digitalis the pulse became regular but signs of congestion increased. The only other therapy has been four doses of mercupurin. If I continued digitalis therapy in spite of the fibrillation which developed would the ventricular rate, which is rapid even during fibrillation, slow down and become more regular? Incidentally, the fibrillation was occasionally replaced by short periods, say thirty seconds, of slow, regular pulse. The only sign of digitalis toxicity was partial loss of appetite.**

Bernard Marcus, M.D., Bronx, N. Y.

ANSWER.—It is impossible to answer the specific question raised, but the principles underlying a proper answer can be outlined in detail. The ranges of digitalizing doses of digitalis and of maintenance doses are now recognized to be wider than had been hitherto supposed. An occasional patient will become digitalized on as little as 5 cat units, will require only 2 units a week as a maintenance dose and will become toxic if 3 units a week is given. On the other hand, an occasional patient can take as much as 30 units during the course of a massive dose technic of digitalization and will require 2 units a day as a maintenance dose and may not show toxic signs on 3 units a day.

It is impossible to say whether the patient described had too much or too little digitalis, but it would seem probable that it was the former. Without an electrocardiogram it would be clinically impossible to determine whether during the periods of fibrillation his rapid ventricular rate was the result of beats all of which were of supraventricular origin or some of which were ventricular extrasystoles. Furthermore, the ST and T changes in the electrocardiogram would give some clue as to possible digitalis intoxication. It should be added that a few patients develop serious toxic digitalis rhythms without even a loss of appetite as a clinical guide to the nature of the trouble.

A relatively small initial dose of digitalis may be given at a time when the patient has had none for some three weeks (approximately 5 cat units). If the signs of congestion begin to improve, 1 unit every other day might be tried as a maintenance dose, modifying this as seems indicated by the progress of the congestive heart failure. If there is no evidence of clinical improvement eight hours after the first dose of 5 cat units, 2 or 3 cat units might be given every twelve hours until the patient begins to improve. A diuresis is one of the frequent early signs of clinical improvement. When this begins, the large doses should be discontinued immediately and smaller ones started, their frequency to depend on the total amount given by the foregoing technic. If, for example, a diuresis begins after 11 cat units has been given in three divided doses, it is probable that the patient cannot tolerate 1 cat unit a day but will do better on something like 5 a week. If, however, a total of 23 cat units has been given in seven divided doses before any evidence of improvement occurs, it is probable that he will require more than 1 cat unit a day as a maintenance dose—probably 9 or 10 units a week.

It is not likely that the patient will develop fibrillation if the digitalis is administered as described. However, if this does occur before signs of clinical improvement occur, two alternatives are open: Maintenance doses of quinidine may be given simultaneously with the digitalis therapy or another preparation may be tried such as squill or strophanthin, of which the former would seem to be the method of choice.

DEXTROSE CONTENT OF POSTMORTEM BLOOD

To the Editor:—**For how long after death and how accurate are blood sugar determinations obtained from cadavers?**

M.D., Massachusetts.

ANSWER.—The dextrose content of postmortem blood is gradually reduced from the time of death. Many factors influence the rapidity of this reduction, such as temperature, enzymatic action and p_H of the blood. Hill estimated that at 37.5 C. the rate of reduction lies between 10.1 and 16.5 mg. per hour, with an average of 12.8 mg. in 100 cc. of postmortem blood. At 27.5 C. the reduction rate was between 4.14 and 6.94 mg. per hour, with the average 5.98 mg.

Disease processes also influence glycolysis. For example, in anemia and leukopenia disorders glycolytic action is retarded, whereas in the leukemias and erythremia there is an acceleration of the process. Furthermore, the dextrose content of postmortem blood at the time of death varies in different conditions. High values are occasionally found in asphyxia, shock, acute coronary occlusion, increased intracranial pressure, diabetes and certain poisons, especially those causing anoxemia. Low postmortem blood sugar is found in starvation, insulin shock, certain liver diseases, such as acute yellow atrophy, and in debilitated and cachectic subjects.

Under the circumstances it is not possible to express an opinion as to the fixed time interval when glucose will disappear. The sugar has been found thirty-six or more hours after death and in favorable cases probably persists until decomposition destroys it.

It is generally recommended that the blood be taken from the left side of the heart as soon as possible after death. Hypoglycemia may be suspected if the tests fail to show dextrose or the substance is present in minimal amounts within two hours after death.

Generally considered, it is the writer's opinion that these tests are of limited value in legal medicine from the point of view both of the cause of death and of the estimation of the postmortem interval.

For a more comprehensive discussion of the subject with the literature, the inquirer is referred to the article on the significance of dextrose and non-dextrose reducing substances in postmortem blood by E. V. Hill in the *Archives of Pathology* **32**:452 (Sept.) 1941.

ALLERGY AND ALBUMINURIA

To the Editor:—I have heard recently of studies on the relationship of allergy to albuminuria. A patient is sensitive on scratch and intradermal tests to a large variety of foods, household contacts and grass, tree and plant antigens (26 out of 45 tested) although he now has only fall hay fever. He had stubborn eczemas in childhood, and is still prone to contact dermatitis. His albuminuria, which began after an attack of massive hematuria, is still quite heavy, eleven months later. He has had several flare-ups of hematuria during the past year following physical strains or colds. However, his blood pressure is never over 130/90 and was 124/84 five years ago. He has never had any anasarca or other manifestations of glomerulonephritis. His plasma proteins, sedimentation rate and nonprotein nitrogen are all normal. Would I be justified in attempting to desensitize this patient with streptococcus vaccine on the basis of attributing his nephritis to abnormal sensitivity to Streptococcus haemolyticus?

M.D., Indiana.

Answer.—In acute allergic reactions, such as serum sickness, a severe prolonged attack of asthma or following an acute anaphylactic reaction, albuminuria is apt to occur as part of the general clinical picture. In the ordinary atopic manifestations, such as rhinitis, asthma or eczema, albuminuria is certainly not found with any degree of frequency. It has been shown experimentally in animals that kidney inflammation may result from bacterial sensitization. Presumably the same phenomenon might occur in man. Bacterial allergy, however, is difficult to prove in the individual case, and in the particular instance cited no data are presented which would give evidence for that possibility. If a focal infection, such as infected tonsils or teeth, is present the proper procedure would be to eliminate the infection. Even when a source of bacterial allergy can be proved, "desensitization" with the bacteria or their products still remains a highly experimental procedure.

PSYCHOMETRIC RATING TESTS

To the Editor:—Could you give me information concerning suitable psychometric tests for adults? When time is limited, the Stanford revision of the Simon-Binet test and some of the other longer ones are not appropriate. I have been using the Kent test with fairly good results. Recently its reliability was questioned by some of my associates; for instance, it was pointed out that the answer to question 20, whose picture is on a two cent stamp? Washington's, is wrong. Of course that may not affect the validity of the rest of the questions and answers. I wonder if there is a revised edition of this test which has been found useful because of its brevity and easy computation. Will you comment on the reliability of this test? Thank you for references on this and other short tests.

M.D., Iowa.

Answer.—The reliability of the Kent EGY is fairly good; that is to say, correlative reliability is not as good as one would like to have it, but it is sufficiently high to obtain trustworthy psychologic ratings. Its greatest limitation is that it is essentially an information test, thereby being a handicap to persons who have had little formal schooling. Several army units have used it and report satisfactory results.

For general purposes, the short form of the Stanford Revision of the Binet-Simon test is most satisfactory.

PREPARATION OF PERTUSSIS VACCINE

To the Editor:—Could you give me information on any difference in prophylactic value of whooping cough vaccine made with human blood and that made with animal blood?

James C. Overall, M.D., Nashville, Tenn.

Answer.—Whooping cough vaccine is used chiefly as a preventive, injected preferably soon after the seventh month of life. Vaccine made with human blood is not "washed" and is reported to contain all the products of the micro-organism. Other vaccines made with horse, sheep, bovine or goat blood is washed to rid it from the alien (animal) protein, injection of which might otherwise sensitize the child or, on subsequent injection of any biologic preparation prepared with the homologous blood, might elicit local or systemic reactions of one kind or another. According to some investigators, "washing" weakens the antigen.

BOXING, TRAUMA AND EPILEPSY

To the Editor:—A young man who has been a professional boxer for several months was placed in 4-F by his Selective Service board. The reason for his classification was that he had epilepsy, and it is my opinion that he should not be in that particular professional sport. I am writing to ask what the consensus is on that subject.

M.D., Wisconsin.

Answer.—On theoretical grounds the profession of boxing is a poor occupation for an epileptic person. Frequent blows on the head cannot be good for the integrity or the function of the brain, as witness the condition called "punch drunk." However, it is surprising but true that an epileptic patient may experience skull fracture and severe brain concussion without exacerbation of his seizures.

PROBABLE TRAUMATIC URETHRAL STRICTURE WITH RECURRENT EPIDIDYMITIS

To the Editor:—A man aged 27, of unusually rugged type, doing the hardest kind of work in the oil fields, has just been discharged from the hospital (two days) with the diagnosis of gonorrheal epididymitis. He has three healthy children; the youngest, 14 months, does not suggest syphilis. He denies venereal disease and, after talking to him and his wife, I am inclined to believe this. There is no urethral discharge; therefore there is nothing to examine there. The hospital chart states "No laboratory work necessary," so I do not know on what the diagnosis was based. The patient gives the following history: At 10 years of age he fell astraddle of something and passed blood for a few days. At 14 years of age he began to have attacks of swelling and pain in the scrotum, apparently involving the epididymis, from his description. He has had such attacks for twelve years up to the present time on an average of once a month, he says. Fourteen months ago his wife was delivered by cesarean section because of placenta previa. To avoid another pregnancy the patient had vasectomy done a year ago. He has continued to have his attacks of pain and swelling in the scrotum, and the present is the most severe attack he has had. The right testis is much swollen—about the size of a goose egg—and is moderately tender. The epididymis can be felt, is enlarged and is exquisitely tender. The swelling at the testis is not a hydrocele. He has one enlarged inguinal gland on the left. His temperature is 100 F. The white blood count is 6,000. He had mumps when a child. The mild attacks at frequent intervals have continued since the vasectomy. On account of these recurring attacks I would be inclined to advise removal of the right testis but for the fact that, as he tells, two of the mild attacks have been on the left side. To palpation the left testis is normal at present. One detail that puzzles me is why, if this is a gonorrheal infection arising from infected seminal vesicles, it should continue after vasectomy with the same frequency as before.

M.D., California.

Answer.—The diagnosis made on the discharge from the hospital in this case seems highly questionable. In the first place, the diagnosis was not made by following any scientific examination, and the clinical history as presented here is not one of a chronic gonorrheal infection. It would appear that the most pertinent fact in this man's history is that he had a straddle urethral injury ten years ago. The complication resulting from such trauma is, of course, traumatic urethral stricture. One of the most common causes of spontaneous intermittent epididymitis is urethral stricture. On the basis of the available facts this man most certainly should have a careful investigation of his anterior urethra for stricture and careful investigation of his prostate and seminal vesicles for infection.

To be sure, an adequate vasectomy should protect the epididymis from descending infection, but in the presence of continued epididymitis one must think of the possibility that the vas was not resected on one or both sides or that residual infection remains on one or the other epididymis even after the subsidence of acute local symptoms.

Under no consideration should orchiectomy be thought of in a case like this, but occasionally there are indications for epididymectomy under similar circumstances.

THE CHEMICAL REACTION OF PERSPIRATION ON PEARL ARAGONITE

To the Editor:—Relative to the answer given to Dr. Putnam's inquiry on the effect of skin secretions on pearls (May 20, 1944 issue of The Journal) I wish to state that an erroneous statement is made when it is said that perspiration will not harm pearl aragonite. During the past five years, as director of the Bureau of Natural Pearl Information, an organization supported by forty retail and wholesale jewelry firms, I have handled, inspected, and tested thousands of pearl necklaces of both cultured and natural origin. Among the many necklaces tested, samples of pearls have been found which had lost their original sphericity through strictly chemical processes. This particular problem was first investigated when I was an incumbent on the Pearl Fellowship, Mellon Institute of Industrial Research, 1938-1940. To cite a simple experiment, one has only to immerse a pearl necklace in distilled water and leave it there for a few days. Carbon dioxide will be absorbed from the air, with the result that the distilled water will become mildly acidic. Under certain conditions the pH of the water may get to be as low as 5. On removing the pearls after their submersion, one finds that they are completely white, having lost their original luster and orient. Solution of the calcium carbonate of the pearl has ensued as a result of chemical reaction. Since distilled water is not perspiration, let us consider the analyses of human sweat, as made by Mosher (*J. Biol. Chem.* 99: 781, 1932) and by Vass and McSwiney (*J. Soc. Dyers & Col.* 46: 190, 1930). Sweat was obtained from 4 obese women and the pH of each sample determined. Mosher found the pH to be 5.52, 5.48, 5.39 and 5.77 respectively. Since a neutral solution is taken as pH 7, the figures here given are definitely on the acid side. Vass and McSwiney collected 583, 540, 470, 440, 534, and 498 cc. of perspiration from as many individuals. The pH of these solutions was 5.42, 5.65, 5.02, 5.18, 5.17 and 5.47. The pH values are again those of an acid medium. These authorities give complete chemical analyses of the perspirations examined and should be consulted for the exact acid constituents found. Incidentally, the amount of sweat exuded by stout persons may be twice that formed by normal individuals under the same conditions. The evidence presented here is the real answer to Dr. Putman's inquiry.

A. E. Alexander, Ph.D., New York.